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## Original Communications

### STREPTOMYCIN IN THE TREATMENT OF INFLUENZAL MENINGITIS

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THE observations of Gasperini in 1890, first called attention to the fact that certain actinomyces antagonize the growth of other microorganisms, but it remained for Waksman and his associates<sup>1</sup> to investigate this species systematically with regard to production of antibiotic substances. In 1942, Waksman and Woodruff<sup>2</sup> reported on "Streptothricin, a New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria." In 1944, Schatz, Bugie, and Waksman<sup>3</sup> reported a second substance, likewise obtained from one of the actinomyces, namely streptomycin, which was derived from a strain of *Streptomyces griseus* and which proved active against gram-positive as well as gram-negative bacteria. The list of susceptible human pathogens includes at present many members of the genus *Salmonella*, also *Brucella abortus*, *Pasteurella tularensis*, *Mycobacterium tuberculosis*, as well as *Clostridium welchii*, *Streptococcus hemolyticus*.<sup>4</sup>

Although the activity of streptomycin and streptothricin *in vitro* is similar, the former, because of greater activity against certain pathogenic organisms and because of its lesser toxicity, appeared to present greater clinical possibilities. Reimann and associates<sup>5</sup> have reported its use in the treatment of typhoid fever, and others have likewise had favorable experience with the drug in the treatment of urinary tract infections,<sup>6</sup> tuberculous meningitis,<sup>7</sup> and tularemia.<sup>8</sup>

The present report concerns eight patients ill with *Hemophilus influenzae* type B meningitis who were treated with streptomycin either from the start of therapy or following unsuccessful treatment with other therapeutic agents.

Our first experience with the drug was in the case of a 2-year-old boy who was suffering from meningitis and bacteremia due to *Salmonella panama*. There was no response in this particular case to sulfadiazine, and a trial of streptomycin was suggested by Dr. A. Murray Fisher. The patient was treated and recovery ensued, although it was not certain that the recovery was the result of streptomycin therapy. No toxic manifestations were en-

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countered, however. When, some time later, a patient with influenzal meningitis failed to respond to treatment with sulfonamide and specific rabbit antiserum, the strain of *H. influenzae* isolated from the spinal fluid was tested for sensitivity to streptomycin. The sensitivity was found to be high, and it seemed likely that the infection would respond to treatment with streptomycin.

#### PLAN OF TREATMENT

At the time the first of these patients was treated (December, 1944) there was little prior experience with regard to the clinical use of streptomycin in systemic infections and none with regard to its intrathecal administration, hence the wide variation in the dosage in these patients. In all cases the streptomycin hydrochloride was injected both intramuscularly and intrathecally. The drug was dissolved in normal saline solution in concentrations of 4,000 to 5,000 units per cubic centimeter for intrathecal use, and in concentrations varying between 10,000 and 50,000 units per cubic centimeter for intramuscular use. The intrathecal injections were carried out twice a day, daily or on alternate days, whereas intramuscular injections were given every two or three hours.

The sensitivity of the organisms was investigated in most of the cases and several spinal fluid titers were determined. For both types of determination, a crude serial dilution method was used which consisted in adding a standard inoculum of a young broth culture of *H. influenzae* to varying dilutions of either the streptomycin solution or of the spinal fluid to be tested. Control determinations were set up, employing, in the earlier cases a strain of *Eberthella typhi*, later a strain of *Staphylococcus aureus* (Smith) obtained from the laboratories of Merck and Company, Inc.

Since we wished to obtain information with regard to the efficacy of streptomycin itself in influenzal infections, sulfonamides and specific serum were not used simultaneously with the antibiotic. Either they were discontinued (Case 1) when streptomycin was started, or their administration was begun when streptomycin therapy was thought ineffectual (Cases 4 and 8), or during convalescence (Cases 2 and 5), when sulfadiazine was given only after the patient was apparently well of his original infection. In Case 6 penicillin was used concurrently with streptomycin. In Cases 3 and 7 streptomycin was used to the exclusion of all other antibacterial therapy.

#### CASE REPORTS

CASE 1.—C. R. (Fig. 1). This 6-month-old white child had had a normal birth, and developmental and feeding history was normal until the present illness. The patient had been somewhat fretful five days before admission. Two days before admission the baby began to vomit frequently in a projectile fashion. The following day she had fever and a stiff neck. The day after this the temperature was still elevated, and the patient had a generalized convulsion. That night she became extremely stiff, the eyes crossed, and she seemed depressed but extremely irritable.

On admission her temperature was 100.6° F., pulse 120, respirations 30. The patient appeared to be acutely and severely ill. She was drowsy and listless but became irritable upon manipulation. Her general nutrition was excellent, though she appeared to be somewhat dehydrated. The neck was markedly stiff, both eardrums were red and bulging. Respirations were rapid and regular but shallow in character and a few scattered, moist râles were heard over both lung fields with no definite consolidation. The heart rate was rapid, but

otherwise normal. The abdomen was normal. Reflexes were generally hyperactive. Babinski's, Kernig's, and Brudzinski's signs were present. There was no paralysis of cranial or peripheral nerves. Admission spinal puncture showed 2,200 cells, 90 per cent of which were lymphocytes. Numerous gram-negative pleomorphic rods were seen which showed capsular swelling in type B *H. influenzae* serum.

Bilateral myringotomy was done, and a moderate amount of pus was obtained, which on culture yielded the influenza bacillus as well as a type XIV pneumococcus. *H. influenzae* type B was also recovered from the initial blood culture. The patient received .75 Gm. of sodium sulfadiazine intravenously, 60 mg. of immune rabbit antiserum intravenously, and 40 mg. intramuscularly. About one hour after the administration of the serum, the patient's temperature rose to 106° F., and she became extremely cyanotic. Adrenalin was given and the patient was placed in an oxygen tent and slowly improved. The patient was also given 10 mg. of heparin intrathecally. She received 100 mg. of antiserum during the first twenty-four hours, 50 the second day, 50 on the fifth day, and 25 on the sixth day, making a total of 225 mg. in six days. Spinal fluid cultures remained positive for the first seven days. Blood cultures were sterile after the second hospital day. During the first week the patient was severely ill, was in frank cardiac failure on the third day, and had convulsions on the fifth and sixth days. Her temperature remained elevated during the period of serum therapy, at a level of 102 to 104° F. Heparin was given intrathecally on three days but no significant elevation in clotting time was noted.

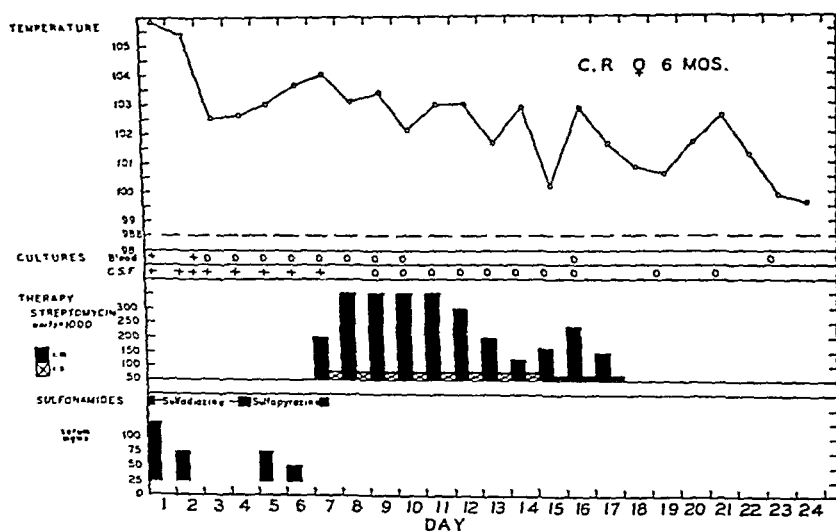


Fig. 1.—Case 1. Good response to streptomycin therapy in a 6-month-old white baby, who had been treated unsuccessfully with sulfadiazine and serum.

We had begun to despair of this patient's complete recovery because of the consistently positive spinal fluid cultures for seven days. The patient's own strain of *H. influenzae* was tested for sensitivity to streptomycin; its growth was completely inhibited by the drug in a titer of 1.2 units per cubic centimeter of culture medium. We felt, because combined serum and sulfonamide therapy had failed to control this patient's infection, that we were justified in resorting to streptomycin therapy. Therefore, on the seventh hospital day, streptomycin was given intramuscularly and intrathecally. Spinal fluid cultures were positive on the day treatment was started and negative thereafter. Streptomycin was given in a dosage of 25,000 units intrathecally for eight consecutive days followed by three intrathecal injections of 20,000 units each. The drug was also given intramuscularly: 25,000 units every two hours for the first five days, 10,000 every two hours for the next two days, 20,000 units every two hours for the next three days, and 10,000 every two hours on the last day.

On the tenth hospital day the patient developed an urticarial rash which seemed to be a manifestation of serum sickness.

The streptomycin given intrathecally was always diluted 1:4. Nevertheless the patient seemed to develop pain at the time when the drug was injected. On streptomycin therapy the patient's temperature rose to about 103° F. every night, although she seemed to be much improved generally except for marked opisthotonus. The spinal fluid count ranged between 200 and 600 cells while streptomycin was being given. It had fallen from 2,200 to 300 cells during the period when serum was given. Streptomycin was administered for eleven days. Two spinal fluid sugars obtained during streptomycin treatment were 16 and 23 mg. per cent, respectively. In view of the patient's generally improved condition they are difficult to interpret. Spinal fluid tested for streptomycin content twenty-four hours after 25,000 units had been given intrathecally showed the presence of 60 units per cubic centimeter.

The temperature fell to normal one week after streptomycin was discontinued. By this time the meningeal signs had disappeared. One week later the cells had completely disappeared from the spinal fluid but the Pandy was still positive.

Thirteen days after streptomycin was discontinued the patient developed otitis media which responded well to sulfadiazine. Culture from the ear showed no *H. influenzae*. The baby was discharged six weeks after admission apparently recovered. She was seen in the dispensary on three subsequent occasions, at which times she seemed to be entirely well.

CASE 2.—J. G. (Fig. 2). This 15-month-old Negro patient was admitted March 6, 1945, with a history of indefinite onset approximately three to four weeks before admission, when he had fever and anorexia with a slight cold and irritability. He was treated by the local physician with one of the sulfonamides in unknown dosage. He failed to improve, ran an evening fever, continued to be irritable, lost weight, and slept poorly. On February 26, he was seen in the Harriet Lane Dispensary with a temperature of 102.6° F. He was thought to have pneumonia. Sulfadiazine therapy was ordered and he was sent home. He returned on March 6 with a temperature of 101.4° F. and a history of drowsiness and a very poor appetite for two days. Lumbar puncture revealed 4,200 cells, 90 per cent of which were mononuclears, and the smear showed organisms which were shown by means of the Neufeld quellung reaction, as well as by culture, to be *H. influenzae* type B.

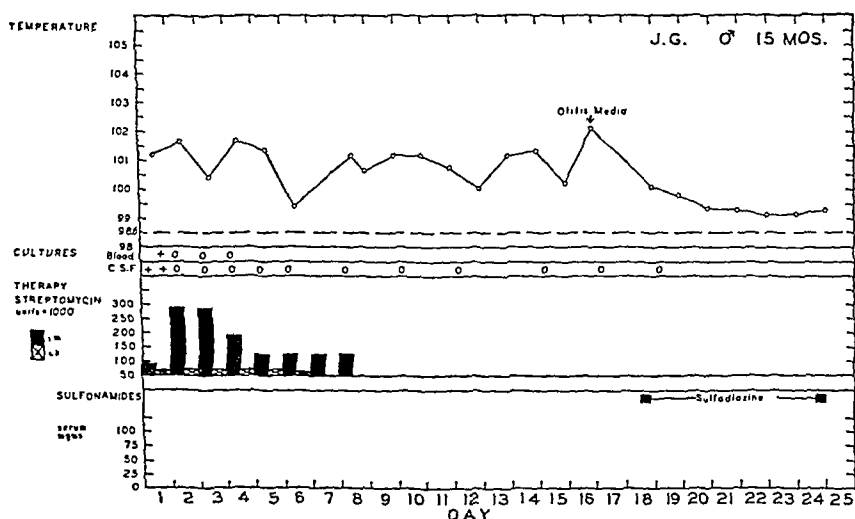


Fig. 2.—Case 2. Prompt response to streptomycin therapy in a 15-month-old Negro infant.

Physical examination showed an irritable and listless child who was moderately and acutely sick. Hydration was good. The cardrums appeared normal, the neck was extremely stiff, and the spine was rigid. Kernig's sign was negative and the remainder of the examination was not remarkable. There were no localizing neurological signs. The hemoglobin was 10.5 Gm. and the white blood cell count 19,000. One sulfadiazine level on admission

was 2.1 mg. per cent. Blood and spinal fluid cultures were positive for *H. influenzae* type B on the day of admission.

Subsequent spinal fluid cultures were sterile on eleven occasions. Nasopharyngeal cultures and cultures from both ears were negative. Blood cultures were sterile on three occasions following admission. The patient was treated with streptomycin for nine days. The first days he received 20,000 units every two hours subcutaneously and for the next five days received 10,000 units every two hours intramuscularly. Intrathecal injections were given for six days. The first five were 20,000 units and the last was 10,000 units. There was no local irritation following any of the injections. The last spinal fluid examination showed a slightly positive Pandey. The cells at all times were chiefly mononuclear cells.

The patient's clinical response lagged behind the bacteriologic improvement, but was fairly satisfactory. The convalescence was complicated by purulent otitis media, not due to *H. influenzae*. This appeared eight days after streptomycin was discontinued. The patient received no therapy other than streptomycin during the treatment of the meningitis.

This then represents a very excellent clinical response in a patient who recovered completely, whose admission blood and spinal fluid cultures were positive and all subsequent cultures were sterile.

The growth of the patient's own strain of *H. influenzae* was inhibited by 1.5 units of streptomycin per cubic centimeter of culture medium.

The spinal fluid twenty-four hours after intrathecal administration of 20,000 units of streptomycin showed a titer of 25 units per cubic centimeter. One-half hour after 20,000 units were injected subcutaneously the blood showed slightly less than 12.5 units per cubic centimeter.

CASE 3.—V. H. This patient was a 16-month-old female, admitted with a history of cough and fever for one month, with stupor and progressive spasticity of five to six days' duration. The present illness began about one month prior to admission with nasal discharge, fever, some enlargement of the cervical nodes, and progressive weakness. The patient was put to bed by order of the family physician. No specific medication was given. She ran a fever during most of the month, usually in the evening. She lost weight progressively, but her condition seemed otherwise stationary until April 7, when she began to develop stiffness of the arms and legs. Stupor developed and for two to three days prior to admission vomiting was frequent. There were no convulsions.

Physical examination showed a deeply stuporous child who appeared almost moribund. Her temperature was 100.6° F. She showed evidence of much weight loss, but of only slight dehydration. The eyes were vacant. The face was scaly, and the skin was dry and exhibited *tache cérébrale*. There were a few scattered, small, erythematous, and follicular papules. The pupils were dilated and did not react to light. The right pupil was slightly larger than the left. The fundi were essentially normal. The eardrums were clear, the neck was stiff, and respirations were irregular with short periods of apnea. There were no significant findings in the chest. The patient maintained extension of the legs, the arms were flexed and hands clenched. The tendon reflexes were generally hyperactive, but somewhat more so on the left. There was clasp knife rigidity. Tonic neck reflexes were present. Babinski's sign was present bilaterally. There was no clonus. Occasional twitchings were noticed about the corners of the mouth.

The hemoglobin was 9.3 Gm. The white blood cell count was 25,000. The spinal fluid showed 600 cells on admission, all mononuclear, and also gram-negative rods which proved to be *H. influenzae* type B. The patient's initial blood culture yielded the same organism, and the nasopharyngeal culture showed both the *influenzae* bacillus and a type VI pneumococcus.

The patient received intrathecal injections of 25,000 units of streptomycin each day for four days, and intramuscular injections of 25,000 units every two hours. The total dose of streptomycin was 100,000 units intrathecally and 1,025,000 units intramuscularly. The spinal fluid culture, positive on admission, was negative on the next three days. However, the patient lost ground steadily and died on the fifth hospital day. The post-mortem blood culture was sterile, but the spinal fluid obtained after death was again positive for *H. influenzae*.

This strain of influenza bacillus was inhibited in its growth by 5 units of streptomycin per cubic centimeter of culture medium

The brain at post mortem examination showed an extensive purulent meningeal exudate which, in places, appeared to be organized

CASE 4—N W (Fig 3). This 8 month old white female infant was referred to the Harriet Lane Home by Dr Margaret Handy of Wilmington, Delaware. The present illness began, about eight or nine days before admission to the hospital, with an upper respiratory infection. Fever developed four days later, and the patient became increasingly drowsy. On the day of admission, April 15, 1945, she began to have convulsive movements of the right arm and leg. She had been taking feedings well and had not vomited. A lumbar puncture performed before admission to the hospital showed cloudy spinal fluid. Before the organism was identified, the patient received two injections of penicillin and 0.3 Gm of sulfadiazine.

The temperature on admission was 102.5° F, pulse 160, respirations 40. The patient was a chubby infant whose excellent nutrition stood in marked contrast to her semistuporous state. There were constant clonic, convulsive movements of the right arm and the right side of the face and tongue. She responded very poorly to painful stimuli. Meningeal signs were moderately well developed and there were generally hyperactive reflexes which were most marked on the right side. The eardrums were red, thickened, and bulged slightly. There was a moderate pharyngitis. The heart was not enlarged, but the sounds were of only fair quality. There was a high pitched blowing systolic murmur heard over the entire precordium. The remainder of the examination was not remarkable.

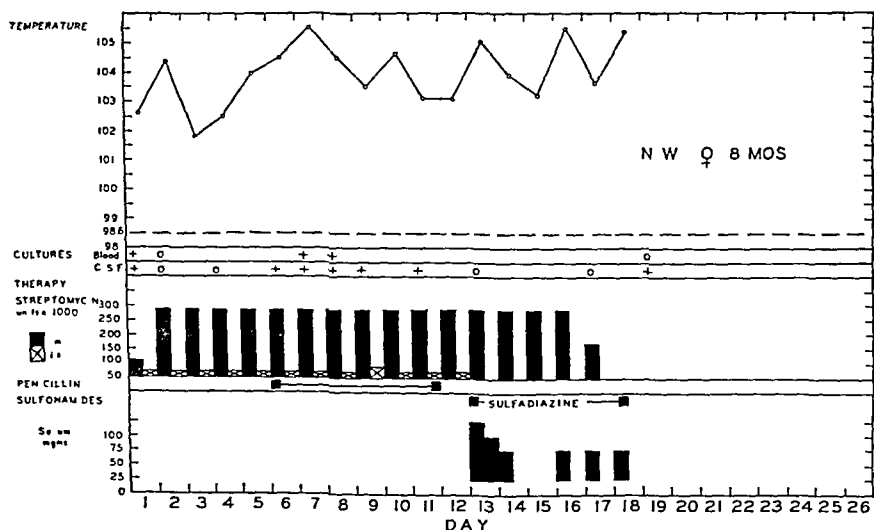


Fig 3—Case 4. Results of treatment of an 8-month-old white infant who, despite large doses of streptomycin early in the course of her illness, developed a drug-fast strain of *H influenzae* and died despite later treatment with serum and sulfadiazine.

Lumbar puncture revealed ground glass fluid containing 980 white blood cells, 90 per cent of which were polymorphonuclear. The unspun, Gram stained smear showed numerous gram negative pleomorphic rods which quelled in type B *H influenzae* antiserum. The organisms far outnumbered the white blood cells on the smear.

The patient was started on streptomycin, 20,000 units intramuscularly every two hours and 20,000 units intrathecally every day. About four hours after the beginning of treatment, she developed a temperature of 104.4° F. and showed peripheral circulatory failure with a very rapid pulse, cyanosis, and cold extremities. Intravenous fluids were given and her general condition improved during the next few hours. She was given a blood transfusion on the second day and bilateral myringotomy was performed. No influenza bacilli were isolated, although pus was obtained. On the second day the patient seemed to be slightly improved.

Blood and spinal fluid cultures on this day were sterile. In spite of her apparent general improvement, the spinal fluid became progressively more cloudy, and on the third and fourth hospital days it clotted shortly after removal. Beginning about the third day a transient flushing reaction appeared after every intramuscular injection of streptomycin. On the sixth hospital day the temperature was elevated to 104.5° F. and it was thought that a bronchopneumonia had developed on the left side. A pneumococcus type XXI was isolated from the nasopharynx at this time. The following day it was reported that the spinal fluid which had previously become sterile was again positive for the influenza bacillus. The organism, which had been inhibited in its growth by a concentration of streptomycin between 1.9 and 3.9 units per cubic centimeter of culture medium, now grew out in 250 units per cubic centimeter. On the thirteenth hospital day sulfadiazine and serum were added to the streptomycin therapy. The child's condition at this time was desperate. She went progressively downhill and died six days later, on the eighteenth hospital day.

Post-mortem culture of the blood was negative, but the spinal fluid yielded the organism on culture. Autopsy showed a severe organizing meningitis over the surface of the brain, most marked at the base. The ventricles were filled with a gelatinous, yellowish-white exudate containing small pockets of fluid.

CASE 5.—R. W. (Fig. 4). This 4-year-old white boy was referred to the Harriet Lane Home by Dr. Margaret Handy of Wilmington, Del., with a diagnosis of influenzal meningitis. The patient developed an upper respiratory infection about two weeks before admission, for which he was given sulfathiazole for two days. He developed another cold five days before admission, but this was disregarded until three days later when he awoke complaining of headache and pain in the eyes which progressed to vomiting. On the day before admission he had photophobia, a chill, and vomited four times. He became progressively more rigid on the day of admission, May 4, 1945. Lumbar puncture done by Dr. Handy revealed the presence of meningitis, and the influenza bacillus was identified by the Neufeld quellung reaction.

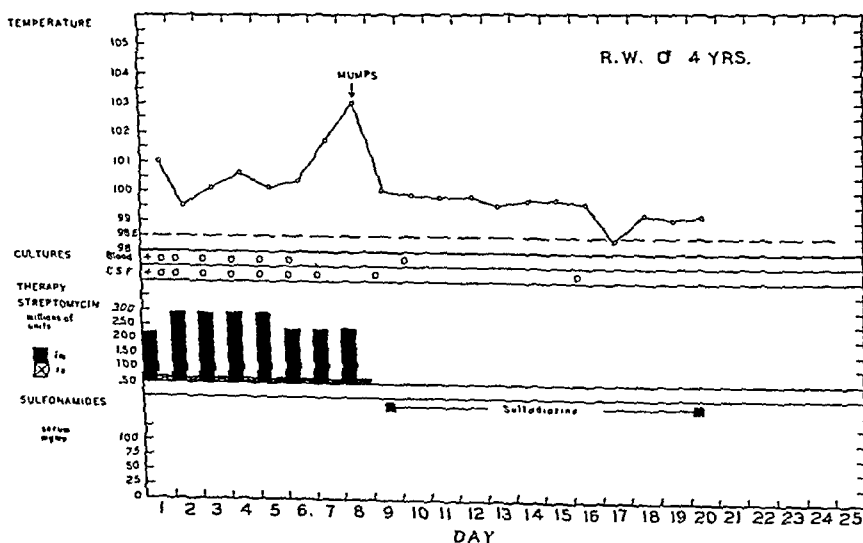


Fig. 4.—Case 5. Results of therapy in a 4-year-old white boy treated successfully with very large doses of streptomycin.

The temperature was 101° F. and the pulse rate was 120. The child was only moderately ill, rational, but somewhat irritable. General physical examination was entirely normal except for moderate inflammation of the pharynx and tonsils, a strongly positive Kernig sign, and a moderately stiff neck. Lumbar puncture showed 800 cells, almost entirely polymorphonuclear. There were a few gram-negative pleomorphic rods seen on the smear. These organisms showed capsular swelling in anti-influenza bacillus serum, type B. Streptomycin caused



venous fluids, plasma, and blood. A spinal fluid culture on the second hospital day and another post mortem, remained sterile.

The growth of this particular strain of *H. influenzae* was inhibited by 3.9 units of streptomycin per cubic centimeter of culture medium. The spinal fluid obtained post mortem contained 130 units of streptomycin per cubic centimeter.

CASE 8.—L. M. (Fig. 6). This 6-year-old Negro male was admitted on May 6, 1945, from the Peninsula General Hospital, Salisbury, Maryland. He had been sick for about ten days with a mild cold which did not change until about four days before admission when he became drowsy. Three days before admission he complained of headache and pain in the back of the neck at which time he was started on sulfonamide therapy. Shortly afterward he was admitted to the hospital where a spinal puncture revealed cloudy fluid from which *H. influenzae* type B was cultured. Following this report the patient was transferred to Sydenham Hospital.

On admission he was found to be a spare, well-developed boy, aged 6 years, who was semistuporous. His temperature was 104° F., pulse 120, respirations 24, and blood pressure 90/60. He was very dehydrated. His pharynx was inflamed. He had a stiff neck and Kernig's sign was present. His ears and lungs were normal. The spinal fluid was cloudy with 4,500 cells, of which 60 per cent were polymorphonuclears; the Pandy was strongly positive; no sugar was present; many organisms were seen on smear and capsular swelling was readily demonstrated with type B *H. influenzae* serum. A blood culture taken on admission was sterile.

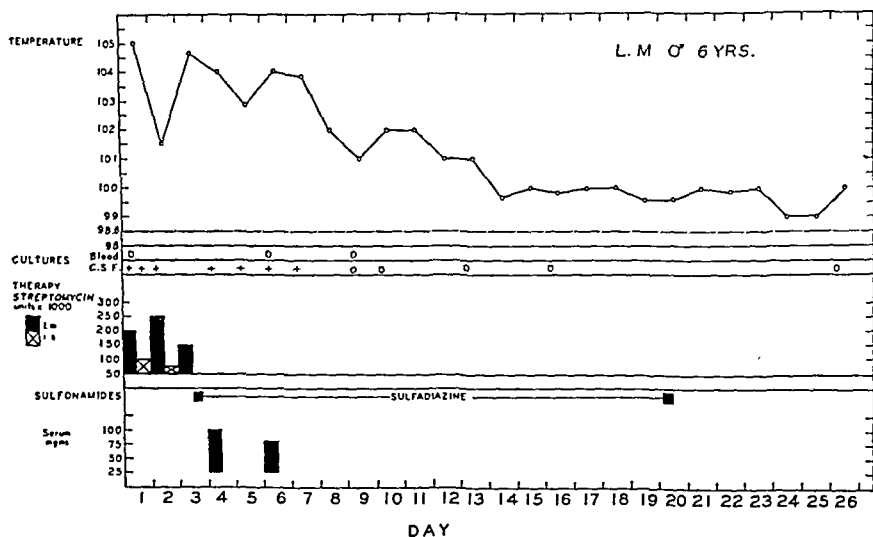


Fig. 6.—Case 8. Six-year-old Negro boy in whom three days of streptomycin therapy failed to sterilize the spinal fluid. With combined serum and sulfonamide therapy he made a good recovery.

The patient was given intravenous fluids; also 25,000 units of streptomycin intrathecally at 9:00 A.M. May 6, repeated at 8:00 P.M. that night, and again at 2:00 P.M. May 7. Intramuscular streptomycin was given on admission, 25,000 units every three hours, and continued for 2½ days.

The patient's temperature fell to 100.4° F. within eighteen hours of admission and his general condition was greatly improved. The spinal fluid examined May 7, i.e., about thirty hours after instituting streptomycin therapy, was ground-glass in appearance, with 2,430 cells, and normal sugar. No organisms were seen on smear but the culture was positive. On May 8, forty-eight hours after instituting streptomycin therapy, the spinal fluid count had fallen to 1,500, of which only 12 per cent were polymorphonuclears, the sugar was again normal, and

no organisms were seen on smear but again the culture was positive. On that day the patient's temperature had risen to 104.6° F. and it was thought inadvisable to delay further drug and serum treatment. Accordingly he was started on sulfadiazine and received 75 mg. of type B *H. influenzae* serum intramuscularly. The spinal fluid culture was positive May 9, May 10, May 11, and May 12. The patient received approximately 60 mg. of rabbit serum intramuscularly May 11. The cultures became sterile on May 14. The patient subsequently convalesced uneventfully.

#### DISCUSSION

The organisms isolated from the patients in this series were shown to be sensitive to amounts of streptomycin small enough to warrant hope that therapeutic levels of the drug could be attained in both blood and spinal fluid. The organisms isolated initially from different patients varied in their sensitivity, so that the concentration of streptomycin necessary to inhibit their growth ranged between 1.2 and 12.5 units per cubic centimeter of culture medium. Spinal fluid levels of streptomycin were determined in only three cases. One patient (Case 7), aged 11 weeks, showed a level of 130 units of streptomycin per cubic centimeter of spinal fluid eight hours after an intrathecal dose of 25,000 units. A second patient (Case 1) aged 6 months, had a level of 60 units per cubic centimeter of spinal fluid approximately twenty-four hours after he had received 20,000 units of the drug intrathecally. A 15-month-old baby (Case 2) showed a spinal fluid streptomycin titer of 25 units per cubic centimeter twenty-four hours after an intrathecal dose of 20,000 units. All patients were receiving the drug intramuscularly at the same time. Since four of our eight patients showed a satisfactory clinical response to the dosage selected, it is believed that adequate drug levels were maintained in both blood and spinal fluid in these cases. Our primary concern was to determine whether or not the drug was effective against the organism and to leave the most economical dosage schedules and possible adjunct therapy to later studies.

Of the four patients who recovered during treatment with streptomycin, it is believed that the drug played the predominant role in the eradication of the infection. While the first patient may have been benefited by the continued presence of circulating rabbit antibody, it seems more than coincidental that the spinal fluid became permanently sterile on the day after the start of streptomycin therapy. Furthermore, it is worth noting that the antiserum titer which had fallen persistently during the first week, necessitating several additional doses of antiserum, became stabilized following the administration of streptomycin. This probably indicates that no polysaccharide was present to combine with antibody in the serum, in other words, that the growth of organisms had been stopped. The disappearance of the bacilli from the blood and spinal fluid of the second patient was directly related to treatment with the drug, and convalescence was entirely satisfactory. In view of the experience with drug fastness in the fourth patient, the fifth patient was treated with very high doses of streptomycin, approximately two to four times higher than those received by the other patients in the series. The persistence of adequate sulfonamide levels during the first day in the hospital may also have played a role in his case. At any rate, dilutions of both blood and spinal fluid were sterile nine hours after the start of streptomycin therapy and his recovery was

dramatic. The fourth patient to have a permanent reversal of cultures had, on admission, residua of a long, untreated, and severe meningitis; in his case, penicillin was used as well as streptomycin, but since penicillin is not effective against most strains of *H. influenzae*,<sup>10</sup> it probably did not contribute to the sterilization of his spinal fluid.

Among these eight patients there were three deaths. The death of the third patient (V. H.) in the series was apparently due to an overwhelming infection. He was only 2 months old, an age at which the prognosis is extremely poor, and he appeared nearly moribund on admission.

The death of the fourth patient (N. W.) after transient clinical improvement was associated with a marked decrease in the sensitivity of the organism to streptomycin, i.e., the development of so-called drug fastness. Within ten days the organism, which originally was inhibited in 3.9 units of streptomycin per cubic centimeter became quite resistant to concentrations of 250 units per cubic centimeter. This experience suggests the need for using large doses of the drug initially in order to avoid the complication of drug resistance. On the other hand, should a patient under treatment not respond satisfactorily, the sensitivity of the infecting organism should again be determined.

The eighth patient in the series (L. M.) unquestionably received the streptomycin in a dosage which was inadequate for his size and age. It is of interest to note, however, that his spinal fluid count decreased; under treatment, from 4,520 to 1,500 cells per cubic millimeter, whereas, his spinal fluid sugar (as determined by the "five tube method") rose from zero to normal. The organisms, though still present on culture, were too few in number to be seen on smear; their sensitivity to streptomycin was unfortunately not determined. It should, however, be noted that the organism, which in the first culture grew only in the unstoppered culture tubes, altered its cultural characteristics following streptomycin therapy, so that it would grow only in the stoppered culture tubes, i.e., under microaerophilic conditions.

Few toxic manifestations were encountered during the treatment of these patients, and none was serious. The increase in meningeal signs during treatment of the first and fifth patients, and the failure of the spinal fluid cell count to fall steadily in patients 1, 2, and 6 after sterilization was effected, seem due to local irritation. The urine, white blood cell count, and hemoglobin showed no abnormal changes. One patient showed an erythema following injections with a dosage of 20,000 units every two hours, and another developed erythema and urticaria when receiving 150,000 to 200,000 units every two hours. The fourth patient in this series had an elevation in temperature and went into shock shortly after the first dose of streptomycin. This reaction did not recur following subsequent injections from the same lot of the drug. Reimann and associates<sup>5</sup> had no reaction other than pain at the site of the injection. Some of these reactions to the drug may have been due to variable impurities in the different lots, as suggested by Robinson and associates.<sup>4a</sup>

In this brief series of patients treated with streptomycin we wish primarily to point out that streptomycin is effective against *H. influenzae* in vivo as well as in vitro. In four patients the drug was extremely effective; in one (Case 4) it

was without effect; one patient was hopelessly ill on admission; one patient showed some response despite inadequate dosage. In view of the rapid sterilization of the blood and spinal fluid in four patients without serious toxic manifestations, streptomycin appears to have a definite, but as yet undetermined, place in the treatment of influenzal meningitis. Further experience will have to determine the proper dosage of the drug and the indications for using it simultaneously with sulfonamides and type-specific rabbit serum.

#### SUMMARY

1. Streptomycin is effective against *H. influenzae* type B in vivo as well as in vitro.
2. Eight patients with meningitis due to this organism were treated. Four recovered, three died, and in one, therapy was given up in favor of sulfonamide and serum.
3. Death in one case was associated with the appearance of drug fastness.
4. Toxic reactions encountered include: erythema, urticaria, augmentation of meningeal signs, persistence of pleocytosis, local pain on injection, and mild shock on initial administration. None of these was serious.
5. Streptomycin is worthy of further clinical trial in cases of infections due to *H. influenzae* type B, and also in cases of meningitis due to bacterial agents which are sensitive to this drug.

The streptomycin hydrochloride used in this study was furnished through the kindness of Dr. D. F. Robertson of Merck and Company, Inc. The potency of the several lots varied between 150 and 300 units per mg. The unit of potency was defined as "the amount of streptomycin which will just inhibit a given strain of *E. coli* in one ml. of nutrient broth or agar." Thus the unit of streptomycin bears no relation to the unit of penicillin. Data supplied by the manufacturers indicated that the lethal dose for 20 Gm. mice varied between 10,000 and 16,000 units according to the lot used. The pH varied between 2.6 and 7.1 in a 2 per cent aqueous solution. In mice the material was found to be pyrogen-free in doses of 5,000 to 15,000 units per kilogram.

#### REFERENCES

1. Quoted by Waksman, S. A.: *Microbial Antagonisms and Antibiotic Substances*, New York, 1945, Commonwealth Fund.
2. Waksman, S. A., and Woodruff, H. B.: *Proc. Soc. Exper. Biol. & Med.* 49: 207, 1942.
3. Schatz, A., Bugie, E., and Waksman, S. A.: *Proc. Soc. Exper. Biol. & Med.* 55: 66, 1944.
4. a. Heilman, R. F.: *Proc. Staff Meet., Mayo Clin.* 19: 553, 1944.  
b. Feldman, W. H., and Hinshaw, H. C.: *Proc. Staff Meet., Mayo Clin.* 19: 593, 1944.  
c. Jones, D., Metzger, H. J., Schatz, A., and Waksman, S. A.: *Science* 100: 103, 1944.  
d. Robinson, H. J., Smith, D. G., and Graessle, O. E.: *Proc. Soc. Exper. Biol. & Med.* 57: 226, 1944.  
e. Waksman, S. A., Bugie, E., and Schatz, A.: *Proc. Staff Meet., Mayo Clin.* 19: 537, 1944.
5. Reimann, H. A., Elias, W. F., and Price, A. H.: *J. A. M. A.* 128: 175, 1945.
6. a. Petroff, B. P.: Conference on Streptomycin, Rahway, N. J., June, 1945, Merck and Co., Inc.  
b. Greer, P. H.: *Ibid.*  
c. Aberhart, C.: *Ibid.*  
d. Shearer, T. P.: *Ibid.*
7. Cooke, R. E., and Dunphy, D. L.: (In press).
8. Foshay, L., and Pasternack, A. B.: *J. A. M. A.* 130: 393, 1946.
9. *Virus and Rickettsial Diseases*, Harvard School of Public Health Symposium, 1940: 324.
10. Hobby, G., Meyer, K., and Chaffee, E.: *Proc. Soc. Exper. Med. & Biol.* 50: 277, 1942.

## INFLUENZAL MENINGITIS

### REPORT OF THREE CASES TREATED WITH STREPTOMYCIN AND SULFADIAZINE

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INASMUCH as the use of streptomycin in the treatment of influenzal meningitis is in its infancy, we are presenting its use, concurrently with sulfadiazine, in three infants, aged 9 months, 16 months, and 15 months, in whom rapid recovery was obtained in the presence of severe influenzal infection of the meninges. The streptomycin was used both intrathecally and intramuscularly with no evidence of toxicity or undue reactions. Recoveries were complete in all three cases with no evidence of damage to the nervous system.

CASE 1.—J. D., a 9-month-old white male, was admitted to the hospital Feb. 14, 1946, with a history of having been ill for three days with anorexia, vomiting, fever, and drowsiness increasing to lethargy at the time of admission. The family history was irrelevant; the past history was noncontributory.

Examination revealed an acutely ill infant, well-nourished, lethargic, with stertorous respiration, and opisthotonos. The anterior fontanel was tense; the Kernig, Babinski, and Brudzinski signs were strongly positive. The left tympanic membrane was moderately inflamed. The pharynx was slightly reddened. The eyes showed no abnormal extraocular movements. The pupils were equal and reacted to light. The temperature on admission was 101.8° F. Tissue turgor was poor. Respirations were 40 per minute, and the heart action was rapid, 140 per minute. A presumptive diagnosis of meningitis was made, and a spinal puncture was done. Cloudy spinal fluid was obtained under moderate pressure; 30,000 units of penicillin were injected intrathecally, and 50,000 units of penicillin were given intramuscularly. A clysis of 5 per cent glucose in saline was immediately started, and sodium sulfadiazine, grains 30, was given with the clysis. A maintenance dose of 50,000 units of penicillin, was continued every three hours intramuscularly, and sulfadiazine, grains 7½, with sodium bicarbonate, grains 15, was given orally every four hours. The child was placed in an oxygen tent. On the second hospital day he received 150 c.c. of whole blood intravenously. The general condition appeared improved.

A report from the laboratory gave the findings for the examination of the spinal fluid: white blood count, 3,687; polymorphonuclears, 74; lymphocytes, 26; globulin, 3 plus; glucose, 12; chlorides, 604; total protein, 123; direct smear, *Hemophilus influenzae* type B; culture, *H. influenzae* type B.

On receiving the report of the organism obtained, the penicillin was discontinued and the child continued to receive sulfadiazine. The temperature on the second hospital day reached 104.2° F. and persisted with brief daily remissions, ranging between 100 and 105° F., from February 14 to 25, when the temperature subsided to normal on February 28. The temperature was elevated from March 2 to 10, and again reached normal on March 11, from which time to discharge on April 8, it remained within normal range, except for a febrile bout of four days, March 15 to 20.

The use of streptomycin was instituted on the fourth hospital day; 50,000 µg were given intramuscularly every three hours, from February 17 to 25. Intrathecal streptomycin was given on February 17, 18, and 19: 15,000 µg dissolved in 2 c.c. of saline on the first day and 50,000 µg dissolved in 5 c.c. of saline on the other days.

From the Department of Pediatrics, Coney Island Hospital.

Sulfadiazine was continued from February 14 to March 10; on March 18, it was started again because of fever, and a spinal fluid examination showing: white blood cells, 710; lymphocytes, 95 per cent, globulin, 1 plus; glucose, 52; chlorides, 675; total protein, 120. March 19, the child developed a typical drug rash due to sulfadiazine, and it was necessary to discontinue the drug. Streptomycin was then used intrathecally, 50,000  $\mu$ g on March 19, and 25,000  $\mu$ g on March 21, and intramuscularly in doses of 50,000  $\mu$ g every three hours on March 19, 20, 21, 22, and 23. The child improved rapidly and the temperature remained normal after this relapse, until discharge. The infant was discharged on April 8, as clinically cured; there were no evidences of nervous system involvement.

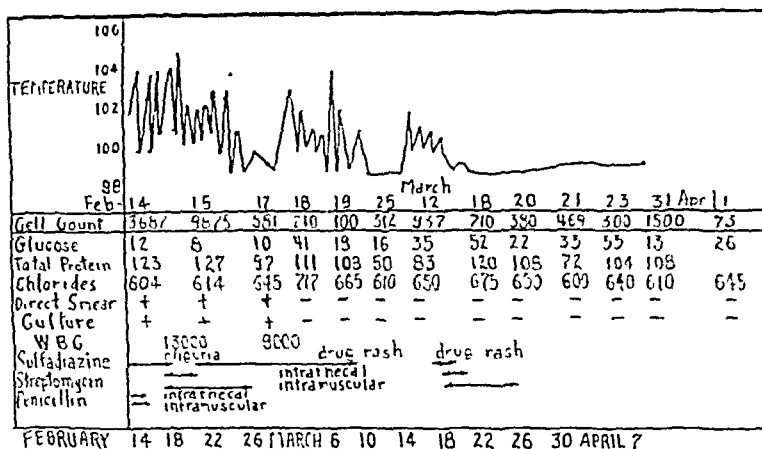


Fig. 1.

CASE 2.—A. H., a 16-month old white female, admitted to the hospital at noon March 19, 1946, had been well (with a negative family history) until the day preceding admission, when the mother noticed that the child appeared sleepy, refused to eat, and vomited several times after taking fluids. The morning of admission the child developed convulsions, and was admitted while in a convulsive seizure.

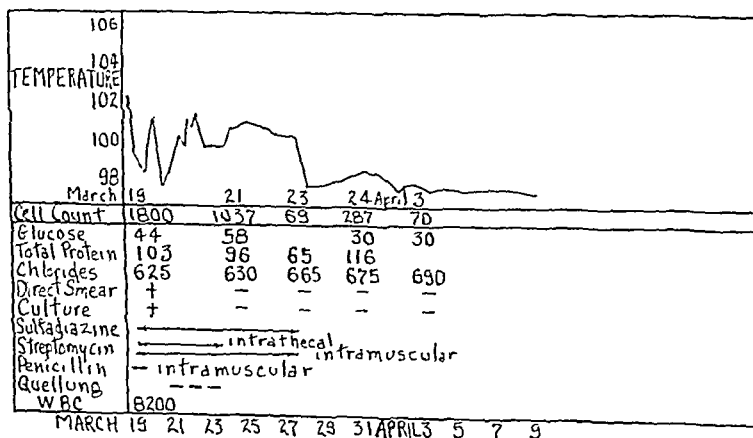


Fig. 2.

Examination revealed a well-nourished white female, cyanotic, with cold clammy skin, temperature 102.2° F., pulse 200, respirations 66. There was generalized twitching of extremities, and noisy tracheal rales. The eyelids were closed; eyeballs rolling; pupils were

equal and small. There were no abnormal reflexes. The ears, nose, and throat were normal. The lungs showed many coarse râles throughout, and some fine râles were heard at the right base.

Sodium amytal, grains  $3\frac{3}{4}$ , was given intravenously to control the convulsion, 3 c.c. of 25 per cent magnesium sulfate were given intravenously, and the patient was placed in an oxygen tent. During examination, a diarrheal stool was voided.

The admission diagnosis included the following possibilities: acute toxicosis, sepsis, pneumonia, and meningitis. A spinal puncture was done while the child was in the admitting room, within four hours after admission, and a cloudy fluid was obtained under 12 mm. pressure. While awaiting a laboratory report, penicillin, 100,000 units, was given intramuscularly; adrenal cortate, aqueous extract, in doses of 3 c.c. was ordered every two hours until reaction; and an intravenous was started with Hartmann's solution; sodium sulfadiazine, grains 30, was given intravenously with a maintenance dose of grains 5 with sodium bicarbonate, grains 10 every four hours to be given orally as soon as the child was able to swallow. She was placed in an oxygen tent.

We were fortunate to receive a report from the laboratory within the hour, which identified the organism as *H. influenzae* type B. We then gave streptomycin 100,000  $\mu$ g intramuscularly, and 50,000  $\mu$ g every three hours to March 24; and intrathecally daily for 5 days, 50,000  $\mu$ g the first three days, then 25,000  $\mu$ g for two days. The streptomycin for intrathecal use was given in saline, 10,000  $\mu$ g per cubic centimeter. An x-ray of the chest taken on the day of admission was negative. On the second hospital day, the temperature began subsiding, reaching normal by lysis on the ninth hospital day, after which it remained normal until date of discharge, April 9. On the second hospital day the general condition had remarkably improved, the child was conscious, began to play, and continued to improve rapidly, until well. At no time was there any evidence of toxic reaction to the sulfadiazine or streptomycin. At discharge, the child appeared perfectly well, with no evidence of neurological involvement.

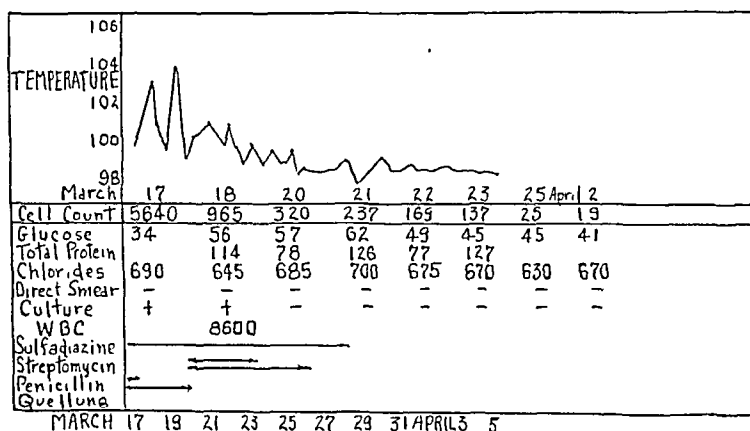


Fig. 3.

CASE 3.—G. B., a 15-month-old white male, was admitted March 17, 1946, with a history of having been well until three days prior to admission, when he became irritable, vomited his breakfast, and had a fever. The following day, he vomited and had a fever of 102° F., which reached 106° F. by evening. At this time he was given Cocadiazene, which he repeatedly vomited. The third day, the temperature ranged between 100.5 and 102° F., and the child appeared restless, was moaning, and developed a swelling over the anterior fontanel. The physician treating the case advised hospitalization because of this swelling and thought a spinal puncture was indicated.

Examination revealed a well-nourished infant, apparently not very acutely ill, with temperature of 100° F., respirations 40, pulse 138, conscious, irritable, with a bulging of the

anterior fontanel (moderately tense fluctuation). The anterior fontanel measured 3 fingers by 3 fingers. There was no neck rigidity, no Brudzinski; the pharynx was slightly reddened. There was a small umbilical hernia. On admission, a diagnosis of meningitis and acute pharyngitis was made and the report of spinal fluid examination was awaited.

A cloudy spinal fluid was obtained under no pressure. With the needle in situ, 50,000 units of penicillin dissolved in 5 c.c. of saline were given. Penicillin, 50,000 units, was given intramuscularly, then 30,000 units every two hours. Sulfadiazine, grains 22½, with sodium bicarbonate, grains 45, was given orally, and maintained; and doses of sulfadiazine, grains 8, plus sodium bicarbonate, grains 15, every four hours, chloral hydrate, grains 2½, with triple bromide, grains 10, were given rectally. A subcutaneous clysis of 1,000 c.c. of Hartmann's solution was given.

On the second hospital day the diagnosis of influenzal meningitis was established by the laboratory. Streptomycin was started March 19, 50,000 µg. were given intrathecally on March 19, 20, 21, and 25,000 µg on March 22 and 23. An intramuscular dose of 100,000 µg was given, then 50,000 µg every three hours were given from March 19 to 26.

The temperature was elevated between 100° F. on admission and a high of 104° F. on the third hospital day when it slowly subsided, reaching normal on March 23, after which it remained normal to date of discharge, April 5. Clinical improvement was slow until after streptomycin was used, when the child became rapidly improved, so that on March 21, he appeared much happier, was smiling at visitors, played, took feedings well, and stopped vomiting. The fontanel by this time was normal. On March 20, the patient had a strabismus of the right eye which rapidly subsided. This was interpreted by the ophthalmologic department as due to the infectious process present at the time.

The patient was discharged on April 5 as clinically cured. There were no evidences of toxic phenomena due to the sulfadiazine or streptomycin. There was no evidence of neurological involvement.

#### COMMENT

The final evolution of a series of antibiotics, capable of mastering most or all of the infections, is seemingly within sight. The dream of the universal therapeutic measure may be realized by the present generation of physicians. Streptomycin has come closer to this ideal than any previous discovery. It has shown great promise in the gram-negative group of organisms, in addition to its equal influence on those organisms affected by previously known antibiotics.

In the meningitides, the meningococcus has its present drug of choice, sulfadiazine; while pneumococcus meningitis is influenced mostly by penicillin. In influenzal meningitis, the main test of treatment comes in infants under 2 years of age. Influenzal meningitis recoveries in infants under 2 years of age, before the advent of sulfonamide therapy in 1935, were reported as about 1 per cent. With the well-regulated use of the Alexander Serum and sulfonamide therapy, recovery rates as high as 80 per cent have been reported. The use of penicillin instead of serum was attended by little improvement in mortality figures. When used in treatment of children less than 2 years old, the results with the use of all these antibiotics given alone, or in combination, were poor when compared with the statistics including all age groups.

Streptomycin given in our cases resulted in more immediate results than were observed with any of the other drugs. The astonishing effects were more impressive to those who had the opportunity to observe the sudden dramatic changes occurring within a twenty-four- to forty-eight-hour period. In Case 1, penicillin and sulfadiazine were used with slow progress. The fever persisted



and there were several relapses. The penicillin apparently gave no response and was discontinued. When a severe drug rash due to sulfadiazine appeared, it became necessary to use streptomycin alone. After this was done, there was almost instantaneous response. There were no further relapses with fever, and the patient could be discharged.

The dramatic influence of streptomycin was again clearly demonstrated in Case 2. This 16-month-old infant was comatose and had convulsions on admission. On the second hospital day, the baby sat up in bed, was playful, and showed no further neurological signs. The spinal fluid culture was negative on this day, and the cell count dropped slowly. The third case, a 15-month-old infant, showed equally good response. All three cases made an uneventful recovery without complications of sequelae.

Although the dosage of streptomycin is not established, the use of 50,000  $\mu$ g intrathecally daily until there is a satisfactory response clinically and on laboratory check of the spinal fluid, is indicated in view of the failure of adequate amounts of streptomycin to enter the spinal fluid after intramuscular or intravenous injections. In addition, intramuscular administration of 50,000  $\mu$ g every three hours has been proved sufficient to maintain an antibacterial level in the blood stream. Treatment is continued until a total of 3 Gm. of streptomycin has been given.

The concurrent use of sulfadiazine was, in our series, because of the feeling of insecurity in the use of a new drug alone. It would be impossible for us to rule out the beneficial influence of sulfadiazine. However, should an opportunity offer itself again, and streptomycin be available, we would not hesitate to use this drug alone. Although we do not wish to draw definite conclusions from such a small series, the enthusiasm displayed by those caring for these infants was warranted by the immediate response in those cases in which the drug was started early. The specificity of the drug appeared definite.

#### SUMMARY AND CONCLUSIONS

1. Report is made of the treatment with streptomycin and sulfadiazine of three cases of influenzal meningitis in children less than 2 years old with recovery without complications or sequelae.

2. Fifty thousand micrograms of streptomycin were given intrathecally daily, until spinal fluid cultures were negative and clinical improvement was definite.

3. Fifty thousand micrograms of streptomycin were given intramuscularly every three hours until a total of 3 Gm. was given in each case.

4. Sulfadiazine in large doses was also given.

5. A small series does not warrant definite conclusions. However, the dramatic influence of streptomycin is significant in patients under 2 years of age where prognosis is poor even with the use of the other antibiotics.

We wish to express our appreciation for the cooperation and excellent suggestions given by Dr. John C. Hamilton, Director of Pediatrics, Coney Island Hospital.

REFERENCES

1. Zinkel, H. A., Flippin, H. F., Nichols, A. G., Wiley, M. M., and Rhoads, J. E.: *Am. J. M. Sc.* 210: 421, 1945.
2. Heilman, D. H., Heilman, F. R., Hinshaw, H. C., Nichols, D. R., and Herrell, W. E.: *Am. J. M. Sc.* 210: 576, 1945.
3. Sako, W., Stewart, C. A., and Fleet, J.: *J. A. M. A.* 119: 327, 1942.
4. Smith, M. H. D., Wilson, P., and Hodes, H. L.: *J. A. M. A.* 130: 331, 1946.
5. Alexander, H. E.: *Am. J. Dis. Child.* 66: 172, 1943.
6. Alexander, H. E., and Leidy, G.: *J. PEDIAT.* 23: 640, 1943.
7. Birdsong, M., Waddell, W. W., Jr., and Whitehead, B. W.: *Am. J. Dis. Child.* 67: 194, 1944.
8. Sako, W., Stewart, C. A., and Fleet, J.: *J. PEDIAT.* 25: 114, 1944.
9. Alexander, H. E., Ellis, C., and Leidy, G.: *J. PEDIAT.* 20: 673, 1942.
10. Silverthorne, N.: *Canad. M. A. J.* 52: 252, 1945.
11. Lamm, S. S., and Shulman, B. H.: *J. PEDIAT.* 24: 408, 1944.
12. Herrell, W. E., and Nichols, D. R.: *Proc. Staff Meet., Mayo Clin.* 20: 449, 1945.
13. Editorial: *J. A. M. A.* 129: 1098, 1945.
14. Keefer, Charles: *Telegraphic communications.*
15. Hinshaw, H. C., and Feldman, W. H.: *J. PEDIAT.* 28: 269, 1946.

# TRIDIONE

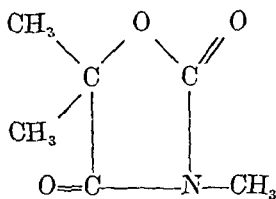
## ITS USE IN CONVULSIVE AND RELATED DISORDERS

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CHICAGO, ILL.

### INTRODUCTION

THIS is a preliminary report of our experience with a new anticonvulsant drug, Tridione,\* in the treatment of certain convulsive and related neurologic disorders.

Tridione (3,5,5-trimethyloxazolidine-2,4-dione) has the following structural formula:



It was synthesized by Dr. M. A. Spielman for use originally as a sedative and analgesic. Although it has analgesic and slight sedative properties in non-toxic doses, it is not as effective as the opium alkaloids or the barbiturates in these respects (Richards, Everett, and Pickrell<sup>1</sup>). It does not affect the blood pressure or the respiratory center. During the course of its pharmacologic investigation, tridione was found to have a marked anticonvulsant effect against metrazol and electroshock in animals (Everett and Richards<sup>2</sup>).

In view of this reported anticonvulsant action in animals, it was decided to observe the clinical effect of tridione in certain neurologic disorders which had shown equivocal or no response to other anticonvulsant medication. A preliminary report,<sup>3</sup> the first to call attention to its efficacy in petit mal epilepsy and in athetosis, has been made by one of us (M. A. P.) before the Chicago Neurological Society, Jan. 9, 1945. Subsequently, Thorne<sup>4</sup> reported tridione to be of some benefit in the control of grand mal seizures and Lennox<sup>5</sup> corroborated its great value in petit mal epilepsy. We are aware that the clinical evaluation of a drug of this type is subject to many pitfalls. The clinical conditions studied are often of the type characterized by spontaneous remissions and exacerbations. Hence, unless patients are observed for relatively long periods, erroneous conclusions might easily be drawn as to the effectiveness of the medication. The conclusions from this study are based to a great extent upon our clinical impressions as well as upon the statistical evaluation of the results.

*Source of Material.*—This study comprises a group of 75 patients with various neurologic and convulsive disorders. They were observed for periods varying from five weeks to sixteen months. Those failing to return for regular visits are excluded from this report. The patients were seen in the Children's

From The Children's Neurology Clinic of the Cook County Hospital, Chicago, and from The St. John's Home and Hospital for Crippled Children, Springfield, Ill.

\*Supplied through the courtesy of Drs. Richard K. Richards and G. M. Everett of the Department of Pharmacology, Abbott Laboratories, North Chicago, Ill.

Neurology Clinic of Cook County Hospital, Chicago, Ill., the Cerebral Palsy Center of St. John's Home and Hospital for Crippled Children, Springfield, Ill., and in private practice.

*Race, Sex, and Age Distribution.*—The distribution of the data by age, sex, and race is given in Table I.

TABLE I. DISTRIBUTION OF PATIENTS BY AGE, SEX, AND RACE

AGE (YR.)	SEX		RACE		TOTAL
	M	F	W	N	
Under 5	4	4	7	1	8
5 to 10	16	14	26	4	30
10 to 15	8	9	16	1	17
15 to 20	3	5	8	0	8
Over 20	8	4	9	3	12
Total	39	36	66	9	75

Of the 75 individuals observed, 39 were males and 36 were females. Only 9 of the total number were Negro. The remaining 66 were white. There was no apparent difference noted in the effectiveness or toxicity of the drug so far as sex and race were concerned.

The youngest patient was an epileptic, one year of age, while the oldest one was a 68-year-old man with tetanus. Approximately two-thirds of the patients were between the ages of 5 and 15 years and only 16 per cent (12 cases) were over 20 years of age. It was in the latter group that most of the toxic effects of the drug, such as dizziness, blurring of vision, and nausea, were encountered.

*Distribution of Material by Clinical Diagnosis.*—The diagnostic categories included various types of epilepsies, cerebral palsies, behavior disturbances,

TABLE II. DISTRIBUTION OF PATIENTS BY DIAGNOSIS AND SYMPTOMS

DIAGNOSIS	NUMBER OF CASES	
<i>Epilepsy</i>	36	
<i>Organic brain disease</i>		17
Grand mal		7
Petit mal		2
Grand and petit mal		8
<i>Idiopathic</i>		19
Grand mal		5
Petit mal		7
Grand and petit mal		4
Psychomotor		1
Psychomotor and grand mal		2
<i>Tetanus</i>	5	
Adults		3
Children		2
<i>Cerebral palsy</i>	21	
Spastics		6
Athetoids		13
Dystonia musculorum		2
<i>Chorea</i>	2	
<i>Parkinsonism</i>	2	
<i>Congenital tremors</i>	1	
<i>Behavior disturbance</i>	8	
With organic brain disease		1
With idiopathic epilepsy		5
Functional		2
Total	75	

chorea, Parkinsonism, congenital tremors, and tetanus (Table II). Nearly one-half (36 cases) of our series were diagnosed as epilepsy, approximately one-half (17 cases) of these being of the type due to organic brain disease, and the remainder, of the idiopathic variety.

Of the 17 patients with organic epilepsy, 7 had grand mal seizures only; 2 had petit mal symptoms only; and 8 had a combination of both grand mal and petit mal seizures. Of the group of 19 patients with idiopathic epilepsy, 5 had only grand mal seizures; 7 had only petit mal seizures; 4 had both grand and petit mal seizures; one had psychomotor attacks alone; and 2 had both grand mal and psychomotor seizures (Table II).

Five patients with tetanus\* were treated, 3 adults and 2 children. There were also 2 children with severe chorea, 2 adults with Parkinsonism, and one with congenital tremors.

Of the 21 children with cerebral palsy, 6 were spastics, 13 were athetoids, and 2 had dystonia musculorum. In children with cerebral palsy, the drug was given with the aim of effecting relaxation.

Of the 8 instances of behavior disturbances, 5 occurred in children with idiopathic epilepsy, one in a child with organic brain disease, and 2 were functional.

*Dosage and Criterion for Benefit.*—The drug was administered generally in 5 grain doses, either in capsules or as an elixir for those unable to take the capsules or their powder contents. The dose varied from 2.5 grains twice a day to 10 grains five times a day. Generally, except for children under 6 years of age, 5 grains three times a day was found to be the optimum dose.

The appearance of drowsiness or other toxic symptoms was used as an indication for reducing the dosage. If benefit could not be obtained below the point of drowsiness, the drug was deemed of no value to the patient.

Benefit was judged from the reports of the patients or their parents, nurses, or attendants, as well as from our own personal observations. Improvement was scored as:

1. *Marked*, when the benefit was dramatic and in all probability due to the drug
2. *Slight*, when the benefit was not dramatic but nevertheless noticeable
3. *No benefit*, when the status remained the same or the condition became aggravated

Whenever possible, electroencephalograms were made before and after starting tridione.†

To the tetanus patients, the drug was administered intravenously and intramuscularly. At first, intermittent dosages of single 5 c.c. ampules containing 1.0 Gm. of tridione, 0.75 Gm. of urethane, and 0.5 c.c. alcohol were used. It was found, however, that the effect of such intermittent dosage was too transient. We, therefore, resorted to the use of a continuous intravenous drip.

\*These patients were on the Children's Neurology Service of Dr. A. Levinson, Cook County Hospital.

†Dr. Fredrick A. and Mrs. Erna Gibbs interpreted the electroencephalograms.

In order to eliminate the possibility that the urethane was a factor in controlling the spasm, 20 c.c. ampules containing 10 Gm. of tridione in 60 per cent alcohol were supplied. A sufficient quantity of this solution was mixed with a calculated amount of saline to maintain a constant intravenous drip over a twenty-four-hour period regulated to deliver 0.5 to 1.0 Gm. of tridione per hour. The highest dosage given was 24 Gm. of tridione in twenty-four hours, without noticeable deleterious effect.

## RESULTS

In order better to evaluate our results, they are presented according to diagnostic categories.

*Epilepsy Due to Organic Brain Disease.*—Of the 17 patients in this group, the etiologic factors were: birth residue in 6, postinfectious encephalitis in 4, lead poisoning in 3, trauma in 3, and influenzal meningitis in one (Table III).

TABLE III. ORGANIC BRAIN DISEASE

CASE	AGE (YR.)	RACE/SEX	SYMPTOMS	ETIOLOGY	BENEFIT WITH TRIDIONE
1	5	W/M	Grand mal	Post-traumatic	Marked
2	3	W/M	Grand mal	Lead encephalopathy	None
3	7	N/F	Grand mal; hemiplegia	Lead encephalopathy	None
4	6	N/M	Grand mal; hemiplegia; shift in cerebral dominance; behavior disturbance	Measles encephalitis	None
5	7	N/M	Grand mal; focal epilepsy	Post-traumatic	Slight
6	15	W/F	Grand mal; focal epilepsy	Post-traumatic	Marked
7	7	W/F	Grand mal	Encephalitis	Slight
8	2	N/M	Petit mal	Encephalitis	Marked
9	21	W/F	Petit mal	Birth residue	Slight
10	1	W/F	Petit mal and grand mal	Birth residue	None
11	6	W/M	Petit mal and grand mal	Lead encephalopathy	Marked for petit mal
12	6	W/F	Grand and petit mal; right spastic hemiplegia	Birth residue	None
13	8	W/M	Grand and petit mal	Birth residue	None
14	12	W/F	Grand and petit mal	Influenzal meningitis	None
15	9	W/F	Grand and petit mal	Birth residue	None
16	6	W/F	Grand and petit mal	Birth residue with hydrocephalus	None
17	11	W/M	Grand and petit mal	Encephalitis	None

Therapeutically, the benefits from tridione in this group were not dramatic. In only 4 of the 17 patients was the improvement noteworthy and greater than on any other type of medication. (Table III.) Of these 4, 2 had grand mal attacks due to head trauma; one had petit mal seizures following an encephalitis, and one had both major and minor attacks as a result of a lead encephalopathy. In all of these patients, tridione was used after all the other drugs employed had failed to control the symptoms. Tridione was, in most cases, added to the previous medication, since it was generally found that tridione

CASE II TABLE 3  
BEFORE TRIDIONE

L.T.



R.T.



L.P.



R.P.



L.O.



R.O.



Fig. 1. A.—(Case 11, Table III). Before tridione: This patient had two to three grand mal seizures per year and twenty petit mal per week. The electroencephalogram shows a marked asymmetry between the hemispheres, with a focus of fast activity in the left parietal area and an atypical wave and spike focus in the left occipital region.

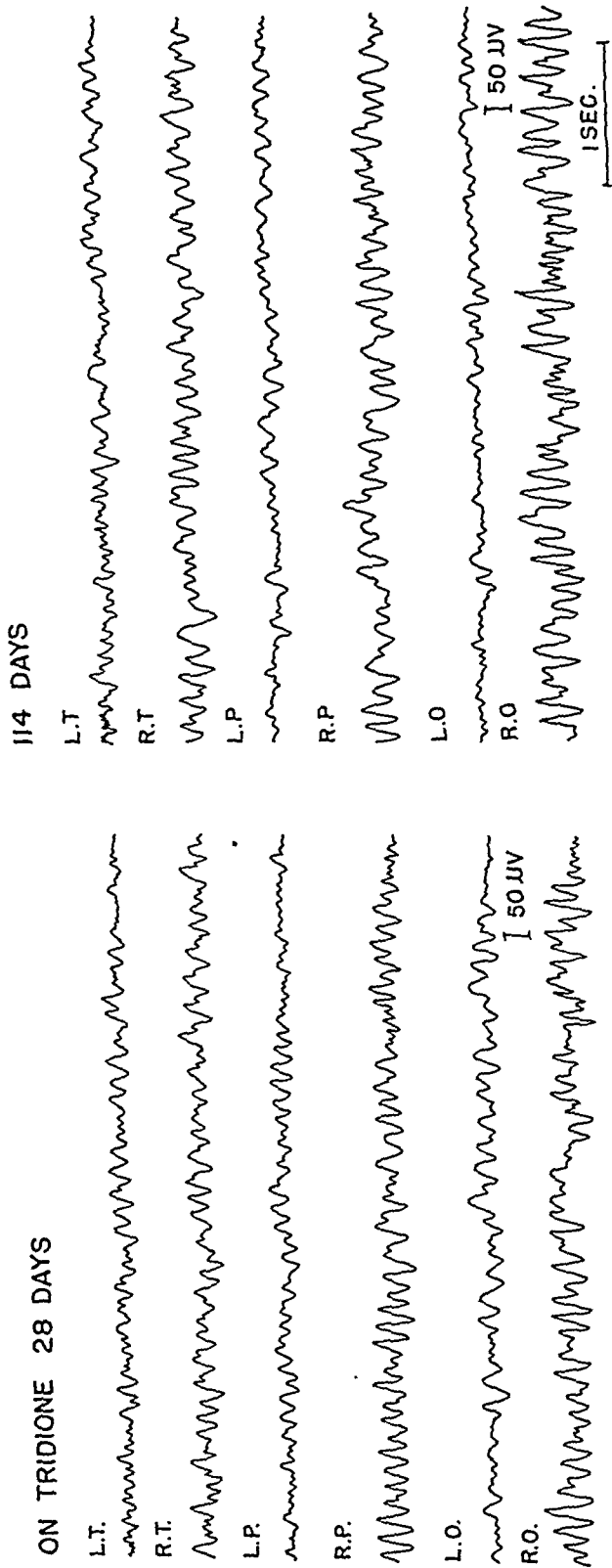


Fig. 1. B.—(Case 11, Table III.) On tridione for twenty-eight days: No grand mal and only one or two petit mal seizures occurred in this period. The electroencephalogram is greatly improved. There are no seizure discharges. The asymmetry is still present but the side of lowest amplitude is on left instead of right and all activity is moderately slow.

On tridione for 114 days: No grand mal and only one or two petit mal attacks per month in this period. The electroencephalogram shows no seizure discharges; the background activity is moderately slow and the asymmetry is still present.



alone did not control grand mal seizures as well as phenobarbital or dilantin alone. Although, in 2 instances (Cases 1 and 6, Table III) grand mal attacks were controlled after the addition of tridione to the previous medication, the greatest improvement was noted in the control of petit mal attacks in the case of which the protocol is given.

#### GRAND AND PETIT MAL DUE TO LEAD POISONING

(Grand mal seizures controlled with phenobarbital and petit mal seizures with tridione)

A 6-year-old white male, J. A. (Case 11, Table III), had a hemiplegia following convulsions associated with fever and coma at 18 months of age. Thereafter he developed repeated convulsions, as many as twenty daily. On phenobarbital medication the grand mal seizures became partially controlled, but petit mal seizures associated with grimacings and pulling up of the arms appeared. At the age of 6 years he was having about twenty such petit mal seizures per week and two or three grand mal attacks per year. The child was mentally deteriorated and difficult to manage.

Although there was no history of exposure to lead, laboratory studies revealed basophilic stippling in the red cells, a lead line in the epiphyses of the long bones, and 450 gamma of lead in 5 Gm. of blood. On the basis of these findings, the diagnosis of plumbism was made.

The child was given 5 grains of tridione three times a day in addition to the phenobarbital he had been taking. Almost immediately, the minor seizures decreased from 20 per week to one or two per week.

The patient remained on the same medication for fifteen months with marked improvement in his behavior and learning ability. During that period he had no convulsions and only one or two petit mal attacks per month.

The clinical improvement was reflected in the electroencephalograms (Fig. 1).

Ten of the 17 patients had no improvement on tridione. In fact, several of them seemed to get worse. In 3 instances, there was some improvement when the patients were given tridione, but the benefits were only slight or temporary, or they had to be maintained by the addition of phenobarbital and/or dilantin.

It thus appears that in epilepsy due to organic brain disease tridione may occasionally be of value in controlling either grand or petit mal attacks. This appears to be especially true in post-traumatic conditions. Of course, convulsions due to organic brain disease are generally more difficult to control by any drug than are "idiopathic" convulsions. However, it is our impression that the effectiveness of tridione as an anticonvulsant in grand mal cases generally is not as great or dependable as that of dilantin and/or phenobarbital, and that it is best used as a supplement in combination with other anticonvulsant drugs in cases not controlled by other drugs.

*Idiopathic Epilepsy.*—Of the 19 patients with idiopathic epilepsy (Table IV), 7 had petit mal seizures only; 5 had grand mal seizures only; 4 had both petit and grand mal seizures; one had psychomotor symptoms consisting of somnambulism; and 2 experienced both psychomotor and grand mal seizures.

In contrast to the organic epilepsies, tridione greatly benefited the majority of the idiopathic epilepsies. Thirteen of this group showed marked improvement with the drug, 3 showed slight improvement, and only 3 showed no improvement (Table IV).

TABLE IV. IDIOPATHIC EPILEPSY

CASE	AGE (YR.)	RACE/SEX	DIAGNOSIS	BENEFIT WITH TRIDIONE
1	12	W/F	Petit mal	None
2	8	W/M	Petit mal	Slight
3	6	W/F	Petit mal	Marked
4	12	W/F	Petit mal	Marked
5	11	W/M	Petit mal	Marked
6	16	W/F	Petit mal	Marked
7	11	W/F	Petit mal	Marked
8	11	W/F	Grand mal	None
9	11	W/F	Grand mal	Marked
10	3	W/M	Grand mal	Marked
11	10	W/M	Grand mal; behavior disturbance; shift in cerebral domi- nance	Marked
12	8	W/M	Grand mal	Slight
13	27	W/F	Grand and petit mal	Marked benefit for petit mal only
14	14	W/F	Grand and petit mal	Marked benefit for petit mal only
15	12	W/F	Grand and petit mal	None
16	9	W/F	Grand and petit mal	Marked for petit mal only
17	27	W/M	Grand mal; schizo- phrenia; psycho- motor attacks	Marked for psy- chomotor and grand mal
18	16	W/F	Grand mal; behavior disturbance; psy- chomotor attacks	Marked for psy- chomotor and grand mal
19	8	W/F	Somnambulism	Marked

(A) *Petit Mal*: The greatest benefit from tridione was obtained in the petit mal group. Inspection of the data reveals that 6 of the 7 patients with petit mal symptoms alone had responded favorably to the drug, 5 of them dramatically, while only one had no improvement at all (Table IV). It should be mentioned that none of these children with petit mal seizures had responded to any of the previous medications such as phenobarbital, dilantin, mebaral, bromides, ammonium chloride, beta-glutamic acid, or other drugs. In fact, the common clinical observation that dilantin and phenobarbital may often precipitate petit mal seizures was, indeed, noted in 4 cases of grand mal seizures. In 3 of these 4 patients, the petit mal seizures were controlled by the addition of tridione to the previous medication. It thus appears that tridione is of value in controlling the petit mal phase of those cases with a combination of both grand and petit mal seizures.

The almost dramatic improvement of cases of petit mal appears to be more constant in the idiopathic form, rather than in that associated with organic brain disease. Table V summarizes our experience with petit mal. Since our experience with 3 patients with psychomotor attacks was similar, they are included in the table. Of the 24 patients with petit mal or psychomotor attacks, 7 of 10 who had associated organic brain disease showed either no benefit or aggravation of symptoms from tridione, while only 2 of the 14 without evidence of such organic brain disease failed to manifest improvement.

(B) *Grand Mal*: There were 11 patients with grand mal attacks of which

TABLE V. PETIT MAL AND PSYCHOMOTOR ATTACKS\*

ETIOLOGY	NUMBER CASES	BENEFIT		
		MARKED	SLIGHT	NONE
Organic				
With grand mal	8	1†	0	7
Alone	2	1	1	0
Subtotal	10	2	1	7
Idiopathic				
With grand mal	6	5‡	0	1
Alone	8	6	1	1
Subtotal	14	11	1	2
GRAND TOTAL	24	13	2	9

\*There were three instances of psychomotor attacks; two with grand mal and all of the idiopathic variety. All three responded with dramatic improvement.

†Grand mal not controlled by tridione.

‡In three of these the grand mal attacks were not controlled by tridione.

5 were markedly improved on tridione, one was slightly improved, and 5 were unimproved or aggravated. It was evident that although the drug might have some anticonvulsant effect, it was not as dependable as phenobarbital or dilantin in controlling major attacks. Its greatest value in controlling grand mal attacks was as an adjuvant or synergic drug to phenobarbital.

It was noted in several instances that whereas tridione might effectively decrease or eliminate major attacks initially the beneficial effect was not sustained, but would tend to "wear off" after a few weeks. Thus, it appears in idiopathic as well as in organic epilepsy that tridione is not a very effective primary anticonvulsant and that its greatest value in this field might be as an adjuvant or synergistic drug, especially with phenobarbital.

(C) *Psychomotor Attacks:* In the 3 patients with psychomotor attacks, marked benefit from tridione was seen in all. In the 2 patients also having grand mal, the drug was effective in preventing major attacks which had been incompletely controlled by phenobarbital alone.

Among the other clinical characteristics of tridione, it was our impression that greater relief from combined petit and grand mal attacks was effected when the drug was used alone, or in conjunction with phenobarbital, and less when used in conjunction with dilantin. Although this was not always the case, tridione and dilantin seemed at times to be antagonistic drugs, especially so far as control of petit mal attacks was concerned.

It was our experience that unlike phenobarbital and dilantin, tridione could be stopped suddenly without fear of precipitating a "status epilepticus." Although there was often a recurrence of attacks when the drug was withdrawn, we have not observed any exacerbation of symptoms greater than before the drug was given. To the contrary, it was often observed that once the attacks were controlled, the drug might be stopped or reduced for days or weeks without any evidences of recurrences. Several illustrative case reports follow:

#### PETIT MAL

(Marked benefit with tridione)

A 12-year-old white girl (Case 4, Table IV) had been having twenty to twenty-five petit mal seizures daily for four years. Neurologic examination was negative except for the fact that hyperventilation precipitated the attacks.

An electroencephalogram was typical for petit mal. The patient was given 5 grains of tridione three times a day and the attacks decreased immediately to two or three per day. The tridione was then increased to 10 grains three times a day and she became completely free from attacks for a period of 3 weeks, the first time this had occurred since the onset of the malady. Then the attacks recurred to about 4 per week. After careful questioning, it was discovered that these attacks usually occurred on Friday, during her dancing lesson. In the excitement of anticipation, she had been failing to take her medicine before dancing. After this was corrected, the frequency of attacks was reduced to two to none per week.

An electroencephalogram taken one week after tridione was started showed a definite improvement over the previous one.

The tridione was gradually decreased to 5 grains three times a day without any increase in the number of attacks, for the past twelve months, to date.

#### PETIT MAL

(Marked benefit with tridione)

A 16-year-old white female (Case 6, Table IV) had had petit mal attacks for eight months. These attacks were limited to the week preceding and one week during her menstrual period. At these times she would have over 100 attacks per day. The attacks could not be precipitated by hyperventilation, but generally by mental concentration as by adding columns of figures, spelling her name backwards, or sewing. She had had two grand mal attacks several years before. She had taken dilantin and phenobarbital without benefit.

The electroencephalograms showed a typical petit mal pattern (Fig. 2).

The patient was given tridione, 5 grains three times a day for about ten days before her menstrual period. This reduced her attacks before the onset of her period to twenty mild attacks on the first day. The next day tridione was increased to 10 grains three times a day and the attacks disappeared completely. She has been entirely free from seizures for the past ten months by taking the drug for the two weeks preceding and during her menstrual period. On two occasions when she ran out of medicine there were recurrences of the petit mal seizures to over 100 per day. This clinical improvement was reflected in the marked improvement in the electroencephalogram (Fig. 2).

#### IDIOPATHIC GRAND MAL EPILEPSY

(Controlled by phenobarbital and tridione)

An 11-year-old white girl (Case 9, Table IV) had been having convulsions since the age of 6 years. They had been increasing in frequency until she had been having an average of three to six attacks daily, most of them at night. She was given phenobarbital, 1 grain three times daily, and her convulsions were reduced to two to three per day. The addition of dilantin 1 grain three times daily resulted in no benefit. As a matter of fact, the attacks became more severe. Dilantin was therefore stopped and tridione, 10 grains three times daily, was added to the phenobarbital. Attacks immediately stopped and have not recurred for eight months in spite of reducing tridione to 5 grains three times daily.

#### IDIOPATHIC EPILEPSY: BEHAVIOR DISTURBANCE; SHIFT IN CEREBRAL DOMINANCE

(Marked benefit with tridione)

A 10-year-old white male (Case 11, Table IV) had convulsive seizures since 6 years of age. He had two to three such attacks per week and an associated increase in his misbehavior. He ran away from home at every opportunity, begged for money, prevaricated, and on several occasions, started fires. He had been expelled from Public School, Orthogenic School, and Parental School. His I.Q. was 120. He was ambidextrous, his dexterity tests showing a preference for the right hand, but greater skill in the left hand.

CASE 6 TABLE 4  
BEFORE TRIDIONE

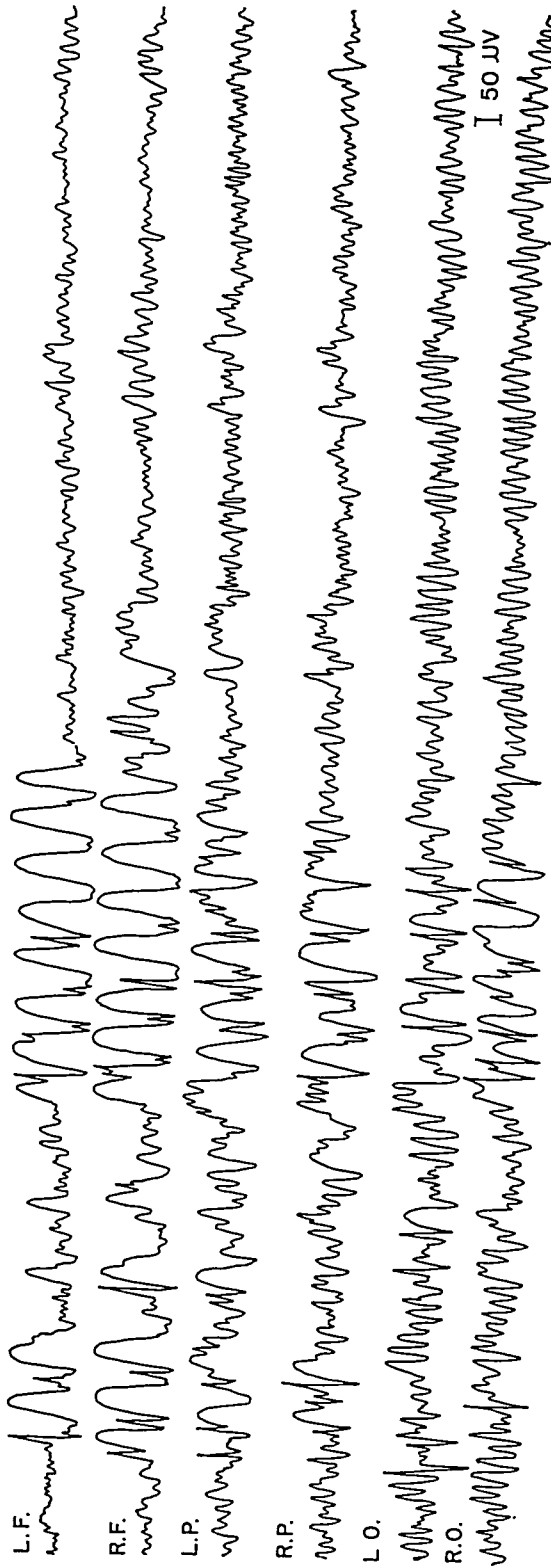


Fig. 2, A.—(Case 6, Table IV.) Before tridione: Patient has had only two grand mal attacks in her entire life, but 100 or more petit mal per day. The electroencephalogram shows frequent three-per-second wave-and-spike discharges of the petit mal type. The background activity is slightly fast.

# ON TRIDIONE II DAYS

L.F.



R.F.



L.P.



R.P.



L.O.



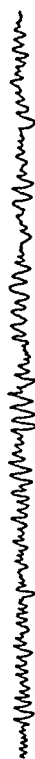
R.O.



I 50  $\mu$ V

# 37 DAYS

L.F.



R.F.



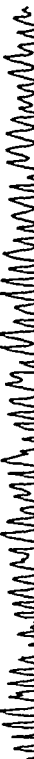
L.P.



R.P.



L.O.



R.O.



I 50  $\mu$ V

I. SEC.

Fig. 2, B.—(Case 6, Table IV.) On tridione for eleven days and thirty-seven days; No grand mal, no petit mal. The electroencephalogram shows no spontaneous seizure discharges, and none could be elicited with hyperventilation. The background activity is still moderately fast.

CASE 17 TABLE 4  
BEFORE TRIDIONE

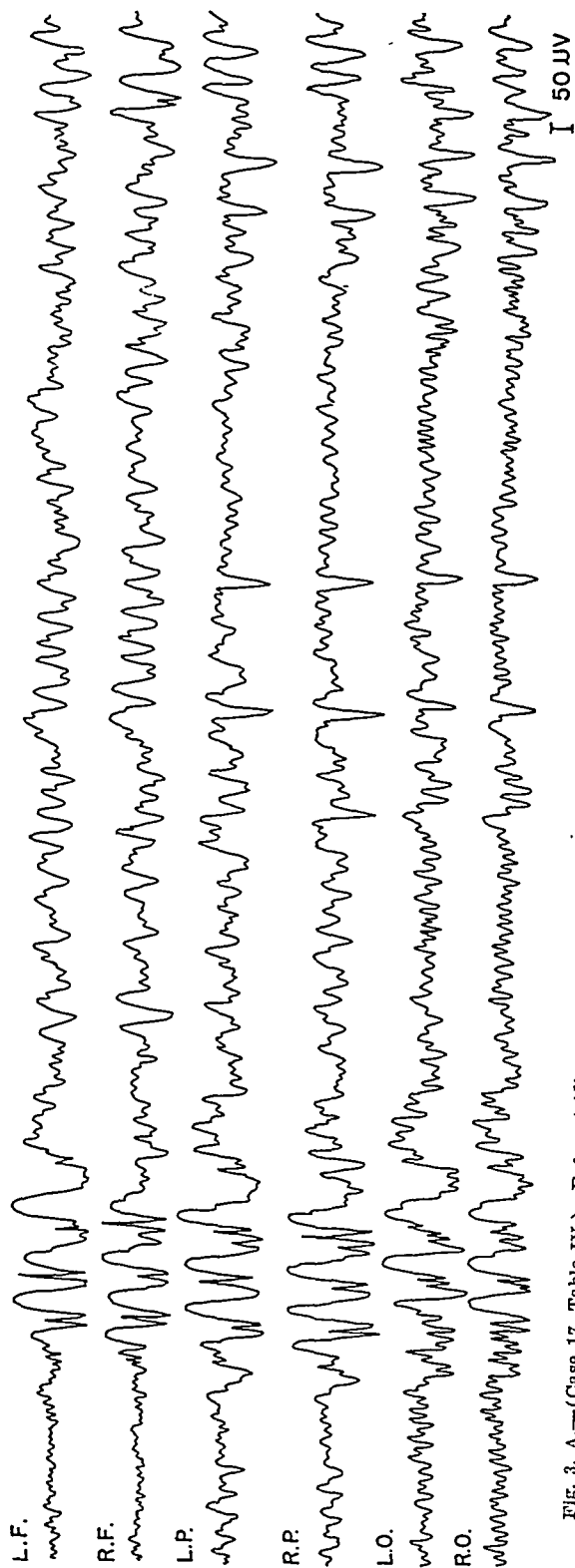


Fig. 3. A—(Case 17, Table IV.) Before tridione: The patient had one attack of grand mal every three weeks, none of clinical petit mal, but approximately three epileptic equivalents (psychomotor seizures) per month. The background activity is exceedingly slow.

# AFTER TRIDIONE 47 DAYS

L.F.



R.F.



L.P.



R.P.



L.O.



R.O.



I 50  $\mu$ V

1 SEC.

Fig. 3. B.—(Case 17, Table IV.) On tridione for forty-seven days: In this period no attacks of grand mal occurred and no epileptic equivalents (psychomotor seizures). The electroencephalogram is greatly improved. No seizure discharges are present, but moderately abnormal fast activity is present in all leads.



Phenobarbital and dilantin were not only ineffectual in controlling either his attacks or his behavior, but in fact, seemed to aggravate his condition. He was given tridione, 5 grains three times a day, and his other medication was gradually withdrawn. His behavior improved dramatically and his convulsions remained controlled for a period of several months. He still has an occasional convulsion and still presents a behavior problem but is much improved. After he had been more than one month without medication, an exacerbation occurred which was controlled by the resumption of medication.

An electroencephalogram done by Dr. E. W. Darrow before tridione was started showed an extremely high potential of hypersynchronous waves. The electroencephalogram taken when the patient was receiving dilantin and phenobarbital showed that the abnormal potentials were much increased. After tridione was started, the electroencephalogram showed a marked and dramatic improvement.

#### IDIOPATHIC GRAND AND PETIT MAL

(Grand mal controlled by phenobarbital; petit mal controlled by tridione)

A 27-year-old white female (Case 13, Table IV) had one or two convulsive seizures per month for the past ten years. The neurologic examination was entirely negative except for a left internal strabismus which was later corrected by surgery.

With phenobarbital and dilantin her convulsive seizures were well controlled so that she had no attacks for eighteen months. However, she developed two to ten petit mal seizures per day. These attacks could be induced by hyperventilation.

She was given tridione and the dilantin was gradually withdrawn. With the combination of phenobarbital and tridione, the petit mal seizures disappeared and the grand mal attacks remained controlled.

#### GRAND MAL: PSYCHOMOTOR ATTACKS: SCHIZOID PERSONALITY

(Marked benefit with tridione)

A 27-year-old white male (Case 17, Table IV) had two to five convulsions per day for the past sixteen years. With bromides and phenobarbital, the seizures decreased to one every two or three weeks. However, he was difficult to get along with at home, always sullen, and could not hold a job. There were times when he would go on drinking bouts without being aware he was doing it. He had a definite schizoid personality characterized by the feeling that people did not want to give him a chance. An electroencephalogram was abnormal with predominant very slow waves with psychomotor and petit mal discharges (Fig. 3).

The patient was then given phenobarbital,  $\frac{1}{2}$  grain, and tridione, 5 grains three times per day, and there was an immediate and remarkable improvement in his attitude and personality. He became happier and was able to get along with his father and mother. For the first time, he showed ambition to go into engineering work. He continued four months without attacks except for one occasion when a gas leak in the home had made the entire family ill. The improvement was reflected in the electroencephalograms taken before and after starting tridione medication (Fig. 3).

*Behavior Disturbances.*—In this series we observed 8 patients with severe behavior disturbances (Table VI). Five of these exhibited marked improvement with tridione, one had questionable improvement, and 2 had none at all. Two of these children, who had been expelled from school because they were too difficult to control, became much subdued on tridione and were readmitted to classes.

We do not willingly wish to convey the impression that tridione changes horns into halos and makes cherubs out of scamps. It is no substitute for psychotherapy and other accepted forms of treatment. However, as a temporary method of sedation in this type of child, it is quite often effective where barbiturates and bromides fail, suggesting that it might have a specific action in some brain center involved in behavior disturbances. In general, the bene-

TABLE VI. BEHAVIOR DISTURBANCES

CASE	AGE (YR.)	RACE/SEX	DIAGNOSIS	BENEFIT WITH TRIDIONE
1	10	W/F	Behavior problem	Marked
2	10	W/M	Behavior problem; grand mal; shift in cerebral dominance	Marked
3	6	W/M	Behavior problem; grand mal	Slight
4	14	W/M	Behavior problem; grand mal	Marked
5	10	N/M	Behavior problem; grand mal	Marked
6	9	W/M	Behavior problem; organic grand mal	None
7	16	W/F	Behavior problem	None
8	27	W/M	Psychomotor attacks; schizo- phrenia; grand mal	Marked

ficial effects in this type of case seem to wear off after a few weeks unless the underlying factors are corrected. Conversely, if the underlying factors are corrected, the drug can be stopped without fear of remission. An illustrative case follows:

#### INFANTILE REGRESSION, DESTRUCTIVE TENDENCIES AND PREVARICATION

(Benefit with tridione)

A 10-year-old white female (Case 1, Table V) developed behavior disturbances at the age of 3 years, soon after the birth of a brother. These disturbances were characterized by thumb-sucking, tantrums, enuresis, prevarication, stealing, and running away from home. She would go to the extent of cutting a screen out of a window to run away from home. Her I.Q. was 100.

She was given 5 grains of tridione three times a day and her behavior improved. She no longer strayed from home and she became more tractable. However, her enuresis persisted. She was placed in the Orthogenic School where her behavior continued to improve even without tridione.

*Cerebral Palsy.*—There were 21 patients seen with this diagnosis. They were divided according to the classification suggested by Phelps<sup>6</sup> into those with pyramidal tract lesions, the spastic group, and those with basal nuclear or other extrapyramidal lesions, which include the athetoids, rigidities, and dystonias. The spastic child exhibits evidence of an upper motor neuron lesion, such as increased deep reflexes, ankle clonus, positive Babinski, and absent superficial reflexes. In addition, he has a "stretch reflex," or reflex contraction of the involved muscle when stretched. On the other hand, in the athetoid child, the reflexes are generally all normal and there is no "stretch reflex." The outstanding features of the athetoid are the continuous involuntary motions and grimacings.

The tension in the children with the spastic type of cerebral palsy is generally involuntary and due to the stretch reflex initiated by the attempted voluntary movement. The tension in the athetoid child is voluntary in nature and due to the attempt to control the involuntary athetoid motion. The tension or spasticity in the rigidity type or those with dystonia musculorum is involuntary in nature and due to a lesion in the basal nuclei which is in some way different from that in the athetoids.

In the treatment of children with cerebral palsy, training is often impossible until the rigidity, spasticity, or tension is released. For this purpose, many methods of relaxation have been employed, e.g., heat, sedation, music,

TABLE VII. CEREBRAL PALSY

CASE	AGE (YR.)	RACE/SEX	DIAGNOSIS	BENEFIT WITH TRIDIONE
1	6	W/M	Spastic	None
2	6	W/M	Spastic	None
3	5	W/F	Spastic	Marked
4	6	W/M	Spastic	None
5	4	W/F	Spastic	None
6	5	W/M	Spastic	Slight
7	18	W/M	Athetoid	Marked
8	2	W/M	Athetoid	Marked
9	26	W/F	Athetoid	None
10	19	W/M	Athetoid	Marked
11	12	W/M	Athetoid	Marked
12	12	W/M	Athetoid	Slight
13	5	W/M	Athetoid	Marked
14	11	W/F	Dystonia musculorum	None
15	16	W/F	Athetoid	None
16	17	W/M	Dystonia musculorum	None (worse)
17	8	W/F	Athetoid	Slight
18	3	W/F	Athetoid	Slight
19	12	W/F	Athetoid	Marked
20	22	W/M	Athetoid	Marked
21	5	W/M	Athetoid	None

wilful voluntary relaxation methods. The usual sedatives are equivocal in their effects. Curare will release the tension, but its action is transient and it may be toxic when used over long periods of time.<sup>7</sup> Although voluntary relaxation is the ultimate goal in training, artificial relaxation may often be of value during the period of training.

In our series, 21 children with cerebral palsy were given tridione. Eight had marked benefit with the drug, 4 had slight benefit, and 9 had no benefit (Table VII). When the results are evaluated in the light of the type of cerebral palsy, it was noted that 4 of the 6 spastics and the 2 with dystonia musculorum derived no benefit from tridione. Of the 2 patients with dystonia musculorum, one was a congenital type unaffected by tridione; the second was an acquired type and became worse on the drug. This patient (Case 16, Table VII) became tense, incoordinate, complained of dizziness, and blurring of vision, and was nauseated. These symptoms were attributed to the toxicity of the drug and tridione was discontinued. Ten of the 13 children with athetosis, on the other hand, showed improvement; 7 were marked and 3 were slight. This would indicate that tridione seems to be beneficial in relieving the voluntary tension of the athetoids, but it is of little value in releasing the involuntary spasm of the spastic or of the dystonic types of cerebral palsy. A typical case report follows:

#### ATHETOSIS

##### (Improvement with tridione)

A 5-year-old white male (Case 13, Table VI) was brought to the St. John's Home and Hospital for Crippled Children, of Springfield, Ill., with such severe athetosis and tension he was unable to sit in a chair. Quinine, phenobarbital, prostigmine, and bromides failed to release the tension. After receiving tridione, 5 grains three times daily, he was able to sit comfortably, move his hands freely, and utter intelligible words. In occupational therapy and speech therapy he was able to respond well to treatment, whereas, previously, no response could be elicited.

*Chorea.*—Two children with chorea were treated with tridione with equivocal effect. Although there seemed to be some sedative action by the drug, we could see no remarkable benefit or any advantage over phenobarbital.

*Parkinsonism.*—Two patients with postencephalitic Parkinsonism, both adults, were given tridione. Both developed side-effects from the drug, with no benefit to the tremors.

*Congenital Tremors.*—One patient, a man 50 years old, with congenital tremors, was given tridione. He had noted that the taking of one or two cocktails (or any alcoholic beverage) had a sufficient sedative action on him to improve his writing from a rather scrawling script to a very steady one. (A similar steadying effect from alcohol is frequently observed in the athetoid form of cerebral palsy.) He noted a similar effect from taking 5 grains of tridione. When he took 10 grains of tridione he developed a slight blurring of vision.

*Tetanus.*—Five patients with tetanus were treated with tridione, 3 adults and 2 children. The drug was administered intravenously with the object of releasing convulsive and respiratory spasms which are often fatal in this condition.

The first patient treated was a child with a very severe tetanus who was admitted to Cook County Children's Hospital in a critical condition. This child was in a coma and had severe and frequent spasms. The intravenous tridione released the spasms, but the child died of a bronchopneumonia. This child received a total of 6 Gm. (90 grains) of tridione in twenty-four hours without apparent ill effects.

Encouraged by this response, tridione was used in the next two cases, both adults, and both with chronic alcohol addiction. A dose of 1.25 Gm. (20 grains) intravenously, controlled the patients for only one-half hour. Hence it was decided to administer the drug by continuous intravenous drip, diluting the tridione in normal saline and regulating the flow to deliver 1 Gm. of the drug every hour after an initial sedating intravenous injection was given. Even this dose of 24 grams (360 grains) in twenty-four hours was ineffectual in controlling the respiratory spasms and both patients died. Since both of these patients were alcoholics, we felt that the alcoholism may have engendered resistance to tridione as it often does to barbiturates.

The fourth patient was a child with mild tetanus. Tridione was administered by continuous intravenous drip of 10 Gm. per day for a period of three days. The convulsions were completely controlled and the child recovered without any ill effects except a mild transient hypertension which lasted about one week. Blood examination and urinalysis revealed no abnormal changes from the drug.

The fifth patient was a Negro male, 68 years of age, who was also a severe alcoholic addict. In spite of the continuous intravenous administration of tridione, the patient died in a respiratory spasm.

In the tetanus cases no definite conclusions can be drawn as to the value of the drug. It seems to be effective in controlling the tetanic spasms in children but not in alcoholic adults. It shows some promise in this condition and should be further investigated.

5. It may be of value in the temporary control of children with behavior disturbances.

6. It is of possible value in the control of the convulsions and respiratory spasms of tetanus when given intravenously.

7. It is of no particular value in chorea, Parkinsonism, or dystonia musculorum.

Regarding its clinical pharmacologic properties, it has been our experience that:

a. Tridione is a safe drug to use since no permanent deleterious effects, addiction, or tolerance were noted.

b. Toxic symptoms are usually mild and consist of photophobia, visual blurring, dizziness, and nausea. They occur more commonly in adults than in children and disappear promptly when the drug is withdrawn.

c. Sudden stopping of the drug in epilepsy does not result in status epilepticus.

d. When used in combination, it is more effective with phenobarbital than dilantin.

e. Chronic alcoholism increases the tolerance to the drug.

f. Since it is least effective in lesions of the pyramidal system and more effective in certain conditions with extrapyramidal lesions, it is suggested that its site of action is probably in the midbrain, and/or areas in the basal nuclei, and/or upon the cortical connecting tracts of these areas.

#### REFERENCES

1. Richards, R. K., Everett, G. M., and Pickrell, K. L.: Pharmacological and Chemical Studies of Tridione With Special Reference to Its Analgesic Action (In Manuscript).
2. Everett, G. M., and Richards, R. K.: *J. Pharmacol. & Exper. Therap.* 81: 402, 1944.
3. Perlstein, M. A.: Tridione. II. Clinical Investigations, *Arch. Neurol. & Psych.* 55: 164, 1946.
4. Thorne, F. C.: *Psychiatric Quart.* 20: 1, 1945.
5. a. Lennox, W. G.: *M. Clin. North America* 29: 1114, 1945.  
b. Lennox, W. G.: *J. A. M. A.* 129: 1069, 1945.
6. Phelps, W. M.: *J. A. M. A.* 117: 1621, 1941.
7. Perlstein, M. A., and Weinglass, A.: *Am. J. Dis. Child.* 67: 360, 1944.
8. Penfield, W., and Erickson, T. C.: *Epilepsy and Cerebral Localization*, Springfield, Ill., 1941, Charles C Thomas, Publisher, p. 134-142.

## A COMPARISON OF THE VITAMIN C IN MOTHERS AND THEIR NEWBORN INFANTS

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NEW YORK, N. Y.

THE plasma ascorbic acid concentration of the newborn infant and of cord blood has been shown to be considerably higher than that of the maternal blood.<sup>1</sup> This has suggested the important concept that the fetus takes its supply of vitamin C whether or not the mother has a sufficient amount. However, as has been pointed out in *Nutrition Reviews*<sup>2</sup> the "plasma ascorbic acid levels are notoriously labile and dependent on recent dietary intake. Determination of tissue vitamin C, or of the values in white blood cell—platelet fraction of blood, would provide more convincing evidence of true maternal-fetal relationships."

We have worked with an intradermal test<sup>3</sup> for vitamin C. This test is based on the intradermal injection of a dye which will be decolorized by vitamin C. Slow decolorization of the dye would indicate that the tissues have an insufficient amount of vitamin C. Rapid decolorization would indicate a sufficient amount.\* In our test enough of a N/300 solution of sodium 2,6-dichlorophenol indophenol is injected to raise an approximately 4 mm. wheal. A skin test time (time for disappearance of dye) of 14 minutes or more suggests a definite degree of tissue unsaturation, from 10 to 13 minutes is borderline, and less than 9 minutes, a normal amount of vitamin C in the body tissues.<sup>3</sup>

### PLAN OF STUDY

A comparison of the vitamin C in the tissues of mothers and their newborn infants was to be made by means of the intradermal test. The intradermal test for vitamin C was done on mothers and their infants as soon after birth as possible. Tests on the infants were repeated every other day until discharge from the hospital. All intradermal tests were done in duplicate. There was no attempt at selection of patients.

### RESULTS

Seventy-seven mothers and their newborn infants were tested. The first test on the infants was done within the first twelve hours after birth. The results are found in Table I. The intradermal test times for disappearance of the dye were practically always shorter in the newborn infant than in the mother. Although thirty-two of the mothers had intradermal test times of 10 minutes or longer, only one infant (Case 73) had longer than 10 minutes. In following that particular infant on subsequent days the intradermal test became similar to the others.

In fact, the intradermal test times in almost all of the newborn infants were within the range that we have come to believe indicates approaching saturation,

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\*Plates of the test appear in J. PEDIAT. 28: 134, 1946.

TABLE I. INTRADERMAL TEST TIMES OF MOTHERS AND THEIR NEWBORN INFANTS

CASE	RACE	MOTH- ER'S AGE YR.	TEST TIME MIN.	SEX OF INFANT	IN- FANT'S AGE HOURS	TEST TIME MIN.	2ND DAY TEST MIN.	4TH DAY TEST MIN.	6TH DAY TEST MIN.	8TH DAY TEST MIN.
1	N	33	19.7	m	1	6.0	5.1	4.3	4.6	2.8
2	N	22	17.4	m	8	3.5	4.5	4.5	4.6	5.9
3	w	35	17.0	m	6	4.1	7.3*	3.9*	7.4*	
4	w	30	17.0	f	0	4.2	4.3	5.3	4.6	3.7
5	N	20	14.8	m	4	4.3	4.6	3.8	7.4	
6	N	27	14.8	f	0	4.3	6.8	5.4	4.6	
7	w	20	14.4	f†	1	4.0	3.3*	3.4*	5.3*	4.2*
8	LN†	37	14.2	m	3	6.4	5.3	5.3	5.2	4.1
9	w	27	13.4	m	7	5.7	5.3*	4.1	4.5	4.8
10	w	20	13.4	m	6	4.7	5.2	4.8	8.4	4.3
11	w	29	12.9	m	1	5.4	3.4	5.3	4.0	
12	w	18	12.5	m	9	4.4	7.3*	5.3*	5.4*	8.3*
13	w	20	12.5	m	12	6.1	4.2*	4.0	5.9	4.0
14	LN;	21	12.3	f	5	7.1	5.4	4.4	4.9	5.9
15	w	23	12.1	f	10	4.5	3.9*	4.6*	4.6*	4.1*
16	w	25	12.1	f	5	7.6	3.9*	4.6*	4.6*	4.1
17	w	21	12.0	f	1	3.3	3.4	5.5	3.4	4.0
18	w	17	11.8	f	7	5.1	6.9*	5.5	4.6	3.3
19	w	25	11.8	m	4	5.3	6.8*	4.9*	4.3*	4.0*
20	w	30	11.3	m	7	5.8	Died 2nd day (heart)			
21	N	19	11.3	m	4	6.1	7.1*	6.9*	5.9	5.3
22	N	21	11.3	m	12	6.3	3.8	4.1	3.3	
23	w	27	11.3	f	0	7.0	3.7*	5.5*	3.5	
24	w	24	11.2	m	2	7.1	4.6	5.5	3.0	6.0
25	w	26	11.2	f	6	7.6	4.0*	5.0*	5.9*	3.9*
26	LN†	35	11.1	f	1	6.9	4.8	6.3	6.7	
27	w	21	11.0	m	7	4.2	2.6*	4.1*	4.0*	2.9*
28	w	30	10.6	f	8	8.3	5.2*	7.1	5.8	
29	w	21	10.5	m	1	3.2	3.7	4.5	3.4	4.4
30	w	22	10.5	f	4	3.3	3.3*	2.6*	4.2	
31	LN†	19	10.1	f	1	5.6	3.4*	7.7*	5.0	4.9
32	w	39	10.1	f	9	5.7*	8.0*	4.7	5.5	5.2
33	w	26	9.9	f	5	5.4	3.7	5.1	3.8	4.5
34	LN†	36	9.2	m	12	3.4	4.0*	4.3*	4.7*	4.7
35	w	28	9.2	f	3	4.1	4.1	3.8	9.1	5.3
36	w	35	9.1	f	5	3.8	3.4	3.9	4.4	
37	N	14	9.1	f	6	3.8	3.5	3.7	3.9*	3.9
38	w	20	9.0	f	4	5.1	3.0*	9.9*	6.3*	4.2
39	w	22	9.0	m	1	4.7	6.6*	5.2*	3.5*	
40	w	34	8.9	f	5	4.5	4.3	5.9	7.2	
41	w	25	8.9	m	1	4.7	3.5	3.8	3.4	3.6
42	w	21	8.9	m	12	5.8	6.1	4.8	4.0	
43	w	39	8.6	f	8	5.7	4.3	4.0	4.4	
44	w	26	8.6	f	4	5.2	4.3	4.2	3.8	
45	LN†	21	8.5	f	7	4.7	5.7*	7.2	6.1	2.6
46	w	34	8.5	f	8	3.4	4.4	4.7	4.7	
47	w	33	8.3	m	7	3.3	4.9*	4.8*	3.0*	2.9
48	w	25	8.3	f	11	5.3	3.7*	4.0*	5.5*	5.1*
49	LN†	24	8.2	m	10	5.1	4.7	4.5	4.4	
50	w	23	8.2	f	2	4.1	4.0	4.3	3.1	
51	w	25	8.0	f	8	4.8	5.7	6.0	3.2	
52	w	34	7.8	m	5	3.1	7.0	4.9	5.5	
53	w	18	7.8	m	6	4.8	4.5	3.1	3.2	6.9
54	w	27	7.7	m	5	4.2	4.8	4.6	6.5	
55	LN;	18	7.7	m	2	4.4	3.3*	3.5	3.3	
56	LN†	28	7.5	m	2	5.1	4.4	3.8	5.4	
57	w	38	7.5	f†	11	9.5	7.3*	5.7*	4.1	
58	w	20	7.5	f	3	4.7	5.7	6.3*	4.2	5.6*
59	w	35	7.4	m	8	4.3	3.5*	5.0*	4.2	
60	N	21	7.3	f	2	3.6	4.2	4.9	5.0	
61	w	27	7.2	f	2	6.1	4.9*	7.1*	4.8	5.2
62	w	21	7.1	m	2	4.5	4.2	5.7	5.3	
63	w	23	7.1	m	0	3.3	8.1	4.8	5.2	5.0

TABLE I—CONT'D

CASE	RACE	MOTH- ER'S AGE YR.	TEST TIME MIN.	SEX OF INFANT	IN- FANT'S AGE HOURS	TEST TIME MIN.	2ND DAY TEST MIN.	4TH DAY TEST MIN.	6TH DAY TEST MIN.	8TH DAY TEST MIN.
64	w	33	6.8	m	5	3.7	6.2	4.5	3.1	5.3
65	w	26	6.7	f	7	3.0	3.9*	4.5*	4.9	4.3
66	LN†	19	6.5	m	2	3.6	4.2	6.0	4.4	
67	w	22	6.5	f	9	3.3	6.5	3.6*	4.1	
68	w	21	6.5	f	10	4.5	4.4*	5.1	4.5	
69	w	25	6.1	f	7	6.8	4.6	5.7		
70	w	21	6.0	m	10	6.2	4.2	5.7		
71	w	33	6.0	m	1	6.4	5.8	4.8	4.1	
72	w	20	5.9	f	4	5.9	4.6*	6.9*	3.9*	5.7*
73	N	19	5.9	m	5	12.0	3.9	7.1	4.8	4.4
74	w	25	5.8	f	7	4.4	5.9	4.0	4.6	
75	LN†	22	5.6	f	11	4.3	4.6	4.6	4.7	4.5
76	w	23	5.3	m	9	3.5	4.6*	2.7*	4.6*	5.0*
77	w	44	5.2	f	6	4.2	3.6*	3.4*	4.7	3.2

\*Jaundiced.

†Eight months' premature.

‡Light Negro.

that is between 4 and 7 minutes. This was true even in the infants of ten mothers whose skin test time was over 13 minutes (definite tissue unsaturation).

## COMMENT

The intradermal test for vitamin C indicates the same maternal-newborn infant relationship as the plasma ascorbic acid levels. The infant tends toward saturation regardless of the mother's tissue concentration. Even where the mother was somewhat depleted, the infant's tissue vitamin C was good. For example, in Case 1, the mother's intradermal test time for disappearance was 19.7 minutes and the infant's was 6 minutes.

The intradermal tests in the infant on subsequent days for a week or more after birth remained approximately the same. The high vitamin C levels are thus not temporary phenomena after birth, but remain constant. In a later report, we shall show how long these vitamin C levels remain high in the infant.

It is difficult to explain how these newborn infants invariably achieve excellent vitamin C nutrition even when the mothers are depleted. There have been several interesting suggestions. Giroud and associates<sup>4</sup> believed that the fetus had the ability to synthesize vitamin C. King<sup>5</sup> thought it was on "the basis of selective conservation of the vitamin in the more vital tissues, such as the pituitary body, during a period of general body depletion." Manahan and Eastman<sup>10</sup> suggested that there was a selective filtration of vitamin C through the placenta. Lund and Kimble<sup>10</sup> have presented good evidence that the placenta acts selectively to retain the vitamin C in the fetus. The entire answer cannot be given and may await working out of such things as nervous-hormonal-vitamin relationships.

This raises the question whether other vitamins act in a similar fashion. It is of interest to mention that in an unreported work that we did several years ago, the thiamine blood values were higher in the newborn infant than in the



mother. Thiamine blood values tend to be more nearly stable than those of ascorbic acid. This suggested that the newborn infant also takes its supply of vitamin B<sub>1</sub> even if it must deplete the mother.

#### CONCLUSIONS

1. A comparison of the vitamin C in seventy-seven mothers and their newborn infants was made by the intradermal test.

2. The vitamin C intradermal test times for disappearance of the dye were always considerably shorter in the newborn infant than in the mother. These results are in agreement with reports of maternal-neonatal plasma ascorbic acid levels.

3. The newborn infant tends toward vitamin C saturation even if it must deplete the mother.

4. Other vitamins, such as thiamine, may act in a similar fashion.

#### REFERENCES

1. a. Concepcion, I., and Camara, S.: *J. Philippine Islands M. A.* 19: 139, 1939.  
 b. McDevitt, E., Dove, M., Dove, R., and Wright, I.: *Proc. Soc. Exper. Biol. & Med.* 51: 289, 1942.
- c. Lund, C., and Kimble, M. S.: *Am. J. Obst. & Gynec.* 46: 635, 1943.
- d. Snelling, C. E., and Jackson, S. H.: *J. PEDIAT.* 14: 447, 1939.
- e. Manahan, C. P., and Eastman, N. J.: *Bull. Johns Hopkins Hosp.* 62: 478, 1938.
- f. Wahren, H., and Rundquist, O.: *Klin. Wehnschr.* 16: 1498, 1937.
- g. Braestrup, P. W.: *Acta paediat.* 19: 328, 1937.
- h. Montero Sierra, B.: *Rev. Chilena de pediat.* 11: 815, 1940.
2. Placental Transfer of Vitamin C, *Nutrition Rev.* 2: 113, 1944.
3. Slobody, L. B.: *J. Lab. & Clin. Med.* 29: 464, 1944.
4. Giroud, A., and associates: *Compt. rend. Soc. de Biol.* 121: 1062, 1936.
5. King, C. G.: *J. A. M. A.* 111: 1098, 1938.

# DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY

## V. STAPHYLOCOCCAL EMPYEMA: THE IMPORTANCE OF PYOPNEUMOTHORAX AS A COMPLICATION

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STAPHYLOCOCCAL infections of the lungs and pleurae merit the particular attention of the pediatrician because of the marked preponderance of such cases in very young children, the difficulties involved in proper treatment, and the high mortality rate. Many older writers did not separate cases of empyema into etiological groups, and it is not until recent years that the unusual features of the staphylococcus as a cause of empyema have been emphasized. The advent of sulfanamide chemotherapy defined the differences between staphylococcal and other types of lung infections more clearly; and now that a more potent antistaphylococcal agent is available, these differences should not be neglected. We wish to emphasize particularly one aspect of staphylococcal empyema—that is, *pyopneumothorax*, or the tendency for air as well as pus to collect in the pleural cavity. This complication occurred with sufficient frequency in our series to warrant its incorporation as a basic feature of the disease. Moreover, it is of sufficient prognostic importance to justify a thorough understanding of methods of diagnosis and treatment.

This paper is a review of the forty-two cases of acute staphylococcal empyema seen at the St. Louis Children's Hospital over the ten-year period from 1934 to 1943, inclusive. This series does not include cases of empyema which developed during the course of staphylococcal sepsis, nor those chronic cases which were admitted for the purpose of obtaining adequate drainage. Cases of empyema following aspiration of a foreign body or those subsequent to surgical lobectomy or pneumonectomy are also omitted. None of the patients received penicillin. With these exceptions, all cases seen during this ten-year period are included regardless of whether or not surgical drainage was used.

The details of the surgical management of these cases were carried out by the Chest Service of the Department of Surgery, under the supervision of Dr. Evarts Graham.

As soon as a sufficient number of penicillin-treated cases have been observed, they will be reported separately.

*The Importance of the Staphylococcus in the Causation of Empyema.*—The relative frequencies with which the pneumococcus, the hemolytic streptococcus, and the staphylococcus were a cause of empyema at the St. Louis Children's Hospital during the past ten years is shown in Fig. 1. Beginning in 1939, when sulfapyridine first came into wide use, the yearly incidence of pneumococcal empyema diminished promptly, where as the incidence of staphy-

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lococcal empyema actually increased. The peak incidences for the latter indicated for the years 1940 and 1942 are due in part, we believe, to rather widespread epidemics of staphylococcal respiratory infections in the newborn nurseries of St. Louis.

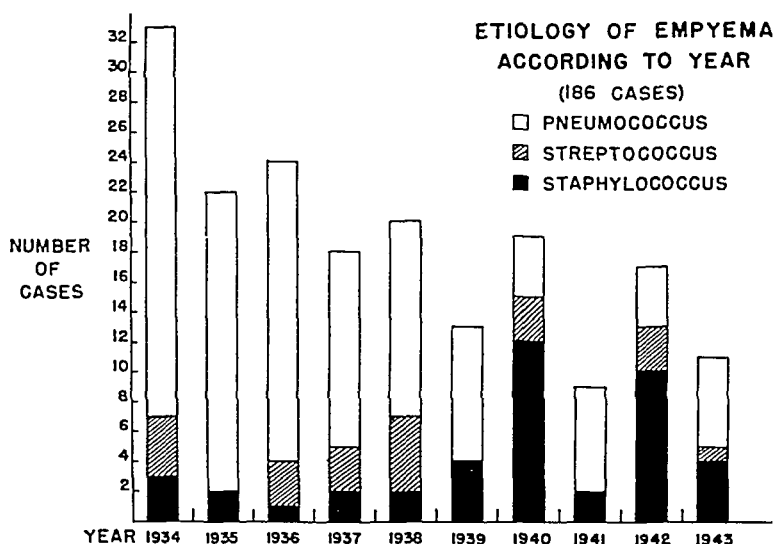


Fig. 1.

Table I is a compilation of data taken from available reports in the literature as to the relative frequency with which the staphylococcus is a cause of empyema in children. Those reports were included which were representative of the pediatric age group as a whole and which gave definite statements as to the causative organism. Papers which dealt exclusively with restricted age groups, with autopsy material, or with surgically treated patients only were omitted, for the purpose of the compilation was to give a picture of empyema from a purely etiological viewpoint as the pediatrician sees it.

*Age Incidence.*—The influence of age as a factor in the determination of the relative importance of the staphylococcus in the causation of empyema is

TABLE I. INCIDENCE OF STAPHYLOCOCCAL EMPYEMA IN CHILDREN

AUTHOR	DATE	TOTAL CASES	STAPH. CASES	PER CENT STAPH.
Spence, <sup>1</sup> N. Y. C. (Babies Hospital)	1913-1920	204	32	15.0
McNeil and associates, <sup>2</sup> Edinburgh	1929	89	2	2.1
McEachern, <sup>3</sup> Winnipeg	1933	75	6	8.0
McEnery and Brennemann, <sup>4</sup> Chicago	1928-1932	168	14	8.3
Hochberg and Kramer, <sup>5</sup> Brooklyn	1929-1936	255	33	12.9
Neuhof and Berck, <sup>6</sup> N. Y. C. (Mt. Sinai)	1928-1932	182	31	17.0
Benson and Penberthy, <sup>7</sup> Detroit	1926-1941	144	9	6.2
Hurwitz and Stephens, <sup>8</sup> San Francisco	1931-1938	60	8	13.3
Lanman and Dimmler, <sup>9</sup> Boston	1919-1939	467	42	9.0
Ellenberg and Martin, <sup>10</sup> N. Y. C.	1930-1940	115	8	6.9
Riley, <sup>11</sup> N. Y. C. (Babies Hospital)	1922-1943	204	22	10.8
Totals		1,963	207	10.5
St. Louis Children's Hospital	1934-1938	117	10	8.5
St. Louis Children's Hospital	1939-1943	69	32	46.4

evident from a comparison of Tables I and II. While many reports in the literature include infants under one year of age, there were only three in which it was possible to clearly determine the incidence of staphylococcal empyema in that age group. Table II presents data which indicate that the staphylococcus accounts for about one-half of all empyema cases in infants under one year of age, as contrasted to 10 per cent for the entire pediatric age group.

TABLE II. INCIDENCE OF STAPHYLOCOCCAL EMPYEMA IN INFANTS UNDER ONE YEAR OF AGE

AUTHOR	DATE	TOTAL CASES	STAPH. CASES	PER CENT STAPH.
Spence, <sup>1</sup> N. Y. C.	1913-1920	53	10	18.9
Neuhof and Berck, <sup>6</sup> N. Y. C.	1928-1932	21	15	17.4
Hochberg and Kramer, <sup>5</sup> Brooklyn	1929-1936	35	14	40.0
St. Louis Children's Hospital	1934-1943	37	27	73.0
Totals		146	66	45.2

The age distribution of the cases of pneumococcal, streptococcal, and staphylococcal empyema seen at the St. Louis Children's Hospital throughout the period covered by this report is indicated in Fig. 2. The largest single group of staphylococcal cases occurred in the group under 6 months of age, and five-sixths of the cases were 2 years of age or less. The staphylococcus accounted for 91 per cent of all cases of empyema in infants under 6 months of age, for 45 per cent in all infants under 2 years of age, but for only 6.4 per cent of empyema cases in children 2 years of age and older.

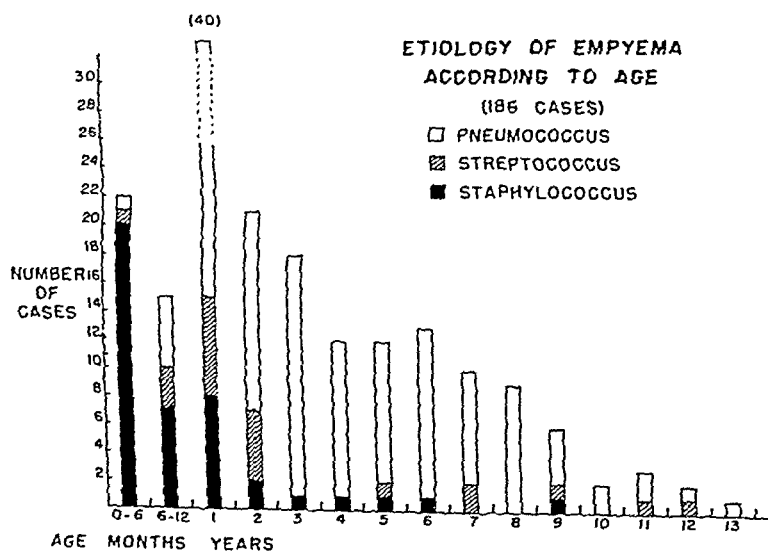


Fig. 2.

*Pathologic Considerations.*—It is generally agreed that the staphylococcus can cause a true primary pneumonia. Since "primary" empyema, for all practical purposes, does not exist, any discussion of staphylococcal empyema must necessarily include the underlying pneumonic process. The studies of Neuhof and Berck,<sup>6</sup> of Macgregor,<sup>12</sup> and of Kanof, Kramer, and Carnes<sup>13</sup>

present the subject adequately. Staphylococcal pneumonia may produce overwhelming toxicity, to a degree that the patient succumbs in a day or two. Under such circumstances the lungs present one or more areas of massive consolidation which are intensely hemorrhagic in appearance. There are sup-pleural hemorrhages, and a serofibrinous pleural effusion is usually present. There is evidence of early suppuration, particularly of the bronchial walls and adjacent alveolar tissue, and there may or may not be a generalized bronchitis. Clumps of staphylococci are found in the affected areas. Later in the course of the disease, the areas of consolidation undergo definite sup-puration, and one or more abscesses form, empyema resulting upon rupture of an abscess through the pleura. Because of the early involvement of the bron-chial walls, and because the abscesses so often ramify, small bronchopleural fistulae are frequently formed, whereupon air enters the pleural space and pyopneumothorax is produced. This can occur at any time during the course of the empyema and may be repeated one or more times as successive ab-scesses create bronchopleural communications. It is because of the method of pleural involvement that pyopneumothorax occurs more commonly in staphy-lococcal than in pneumococcal or streptococcal pulmonary infections.

The sequence of events is described well by Neuhof and Berck<sup>6</sup>:

"The pathologic process in the pleura depends on the site of the pul-monary focus, its extent and the rate of destruction of the overlying parenchyma. In adults the pleural involvement is usually slow and be-nign. The empyema or pyopneumothorax develops gradually in encap-sulated form. Bronchial communications, when present, are generally insignificant, indicating that the abscess in the lung was probably small and subpleural . . . . The collection of pus is in two pockets, with a shelf of infiltrated lung bearing the perforated or non-perforated parenchymal focus lying between them . . . .

"The slow evolution of empyema or pyopneumothorax which has been described as the adult form is also encountered in children. It is not typical of childhood, however, and it is less and less frequently seen as the earliest years of life are approached. *The characteristic lesion in childhood, and more particularly in infancy, is wide rupture of a staphy-lococcic abscess of the lung into the pleural cavity.\** When it evolves slowly, permitting walling-off adhesions to form, pyopneumothorax with little or no displacement of the mediastinum is the result. *On the other hand, total pyopneumothorax with great shift of and tension on the me-diastinum occurs when the abscess develops rapidly with early rupture.\** Never present in adults in our series, this picture occurred in one-third of the children and in almost all the infants."

Thus, the staphylococcal pneumonic process distinguishes itself from the other common types of pneumonia in two respects: Empyema is a very fre-quent sequel, and due to the manner in which the empyema is produced pyo-pneumothorax can often occur.

\*Italics are ours.

*Clinical and Roentgenographic Aspects.*—The onset of the underlying staphylococcal pneumonia in our series of cases was usually gradual: The child had an upper respiratory infection with coryza for several days, followed by fever, cough, rapid respirations, anorexia and listlessness; soon a rather sudden turn for the worse was experienced. The patient rapidly became cyanotic and dyspneic and appeared markedly toxemic. In addition to a typical pneumonic picture, many of the young infants exhibited diarrhea and abdominal distention, the latter to a degree more marked than is usually seen in pneumococcal pneumonia.

In several children the course was fulminating, and the entire chain of symptoms required only twenty-four to forty-eight hours to develop. In some, abdominal distention or abdominal pain together with fever were the presenting symptoms. The dirty, salmon-pink sputum, apparently so typical of staphylococcal pneumonia in the adult, was noted in only one of our patients, an older child. Febrile convulsions occurred in two patients. High fever was a common but not constant feature, especially in the younger infants. Nine patients had admission temperatures between 38° and 39° C., while eight, all under one year of age, had no elevation of temperature on admission to the hospital. The majority of the patients exhibited the usual signs of toxemia: prostration, acute distress, pallor, and the appearances of overwhelming infection. Definite leukocytosis (14,000 to 41,000) occurred in thirty-eight patients, the great majority of whom displayed a definite shift to the left in the Schilling differential count. The remaining four patients had normal or low total white cell counts with marked shifts to the left in the Schilling hemogram; all of these died. Bacteriemia was present in 38.2 per cent of the thirty-four cases in which blood cultures are recorded. The incidence was definitely higher in those patients under 2 years of age (41.4 per cent) as contrasted to children over 2 years of age (20 per cent). Throat cultures were rather inconclusive in this series; they were recorded in twenty-seven cases, and staphylococci were recovered in fourteen of these but were listed as the predominating organism in only seven. In several cases pure cultures of either pneumococci or hemolytic streptococci were recorded.

The physical signs in the chest may be misleading in the young infant. Breath sounds and râles may be heard quite well through an area of empyema fluid despite a dull or flat percussion note. The most suggestive physical finding is the presence of signs of pneumonic involvement of an entire lung field, for empyema will be found in most of the infants who exhibit such findings. In several patients, the physical signs on admission to the hospital were those of massive pneumothorax, the existence of empyema being proved later by diagnostic thoracentesis. When the pneumothorax was limited to a small portion of the lung surface, however, physical signs of it were usually absent.

Fluoroscopic or roentgenographic examination is the only way to arrive at an accurate diagnosis in infants. In uncomplicated staphylococcal empyema, the picture is identical with that of empyema due to other organisms with the exception that the effusion is more frequently seen to occupy an entire lung field. The roentgenographic appearance of pyopneumothorax, however, merits

particular attention. Several characteristic roentgenograms are presented in a subsequent section; unfortunately, due to the critical condition of some of the patients, it was not always possible to obtain roentgenograms at the time pyopneumothorax was most extensive. A large collection of fluid and air with immobility of the corresponding leaf of the diaphragm and a rather

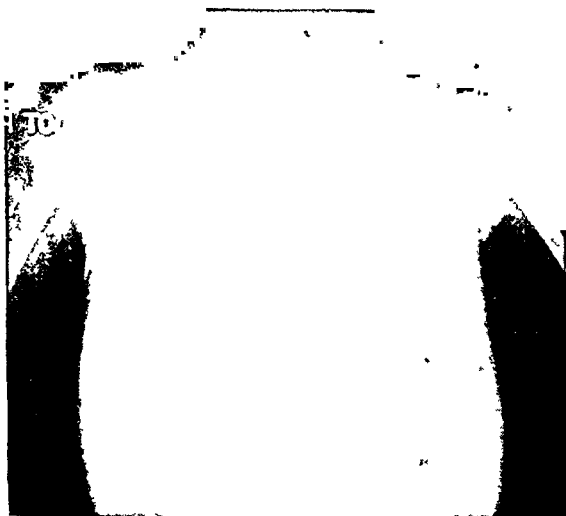


Fig. 3



Fig. 4.

marked displacement of the mediastinum are characteristic findings. The pocket of fluid and air may be rather small, however, if the pyopneumothorax developed late in the disease and was limited by preformed adhesions, or several such pockets may be seen arranged in such a manner as to suggest congenital cystic disease of the lung. The important fact to remember is that

the presence of air and fluid in the pleural space of an infant should immediately suggest staphylococcal disease of the lung.

Now that more potent antistaphylococcal agents are available, the diagnosis of staphylococcal pneumonia should be made early in the course of the disease in order to avert, if possible, the occurrence of empyema. The clinical signs in staphylococcal pneumonia, especially in infants, differ but little from those of pneumococcal pneumonia, and the patient's course during the first day or two of the disease usually offers no unmistakable clue. As previously mentioned, throat cultures are not reliable in small children. The finding of staphylococci in the blood stream and the lack of clinical response to adequate sulfonamide chemotherapy were the main criteria used in this series in the diagnosis of staphylococcal pneumonia. Figs. 3 and 4 show roentgenograms of patients with staphylococcal pneumonia. The areas of consolidation are perhaps a little more extensive and somewhat less well-defined than those ordinarily seen in pneumococcus lobar pneumonia, but the character of the lung shadow is far from pathognomonic.

#### THE IMPORTANCE OF PYOPNEUMOTHORAX

We feel that this extremely important aspect of staphylococcal lung disease has not received the attention it deserves. Isolated case reports of pyopneumothorax occur from time to time in the literature, especially that from England; the majority of these cases ended fatally. There are several large series of empyema cases reported,<sup>1, 5, 9, 10, 11</sup> which include no mention whatsoever of pyopneumothorax; in others<sup>7, 12, 14</sup> it is mentioned briefly but not discussed. McEnery and Brennemann<sup>4</sup> state that "the so-called 'tension-pneumothorax' must be relieved promptly by some continuous method of drainage, or removal of air." The recent report of Clemens and Weens,<sup>15</sup> in which four of the six infants in their series developed pyopneumothorax and manifested striking symptoms as a result of this complication, emphasized the importance of this aspect of staphylococcal empyema. Of the several reports which discuss the problem of pyopneumothorax, both in regard to its seriousness and its proper management, those of Neuhof and Berck,<sup>6</sup> Johnson,<sup>16</sup> and Cohen<sup>17</sup> are noteworthy.

From a consideration of the pathogenesis of pyopneumothorax, which is essentially the result of rupture of a lung abscess into the pleural cavity, thereby allowing air as well as pus to enter, it is evident that the intrapleural air may be present under varying degrees of tension. If the lung abscess develops early and produces a relatively wide pleural rupture, and consequently a large bronchopleural communication, then a massive tension pneumothorax may develop. Under such circumstances the patient always has severe respiratory embarrassment, and sudden death may result. If the pleural rupture is small and occurs later in the course of the pneumonia, the pneumothorax may be limited in extent, due to the existence of pleural adhesions, and only mild symptoms will be produced; or several pulmonary abscesses may rupture through the pleura in succession and thus produce increasing respiratory distress over a period of days. It must be remembered that the less extensive types of pyopneumothorax may at any time, and with alarming rapidity, pro-



gress to the massive tension variety. It should be stressed, then, that every case of staphylococcal lung infection is a potential case of pyopneumothorax, and further, that every instance of pyopneumothorax constitutes a serious danger to the patient.

Pyopneumothorax was definitely demonstrated in seventeen of our patients. This represents a case incidence of 40.5 per cent; thus two of every five patients developed this complication. The age of the patient did not alter the frequency with which pyopneumothorax occurred, the incidence being 40 per cent in children under 2 years of age and 43 per cent in those over 2. These cases represent instances of spontaneous pyopneumothorax only. Air is often introduced purposefully into the pleural space to aid in outlining the empyema cavity, or enters inadvertently during a thoracentesis; under such circumstances no symptoms result.

In our series, four of the seventeen patients with pyopneumothorax exhibited no characteristic symptoms attributable to this complication, the diagnosis being made either by x-ray examination or by noting a rush of air from the pleural cavity at time of surgical drainage.

Three patients had moderate respiratory distress, consisting of dyspnea, rapid respirations, and in one instance cyanosis. Thoracentesis resulted in marked relief of symptoms in two of these patients, and subsequent surgical drainage effected a complete cure. In the other, thoracotomy was done immediately following diagnosis of the pyopneumothorax. Air and pus gushed out under considerable pressure, the patient experiencing immediate relief.

In order to illustrate the symptomatology and proper handling of patients with more marked degrees of tension pyopneumothorax, the remaining ten patients will be discussed individually. All had severe degrees of respiratory embarrassment. Five deaths occurred in this group, and in one instance this complication was the immediate cause of death. In the other four, death was due chiefly to the toxemia produced by the underlying staphylococcal pneumonia; however, pyopneumothorax was a major contributory factor in the death of at least one of these.

#### CASE REPORTS

CASE 1.—R. O., a 1-year-old white male, was admitted on March 9, 1942. He had had a mild upper respiratory infection for the previous week, and on the day of entry he vomited twice and became feverish and irritable. He was seen in the emergency room, his condition was diagnosed as acute pharyngitis, and he was sent home on sulfadiazine medication. Fluoroscopic examination of the chest was negative at that time. Approximately twelve hours later, following two generalized convulsions, the child was returned to the hospital. Examination of the chest now revealed an area of percussion dullness and bronchial breathing at the right base, and a definite shadow could be seen at that area on fluoroscopy. Sputum culture revealed a pneumococcus type IX; blood culture proved sterile, and the spinal fluid was normal.

The baby was given sulfadiazine, but his temperature remained elevated (39.5 to 40.5° C.), and he gradually became dyspneic and rather prostrated during the next three days. Because of the lack of response to chemotherapy, a staphylococcal pneumonia was postulated; skin tests done with the staphylococcus carbohydrate substance were negative, and administration of staphylococcal antiserum\* was begun. During an intravenous injec-

\*The serum used in this series was a special antistaphylococcal rabbit serum, prepared by the Eli Lilly and Company under the direction of Dr. L. A. Julianelle.

tion of serum, the baby suddenly developed respiratory difficulty and cyanosis, and adrenalin was given without relief. Fluoroscopic examination now revealed a density over the greater part of the right lung field, and a small area of pneumothorax was noticed at the costophrenic angle. Within an hour, the area of pneumothorax had increased to a point where about one-third of the right lung field was involved, a slight shift of the mediastinum was noted, and respiratory difficulty increased to an alarming degree despite the administration of oxygen. A needle was then introduced into the right pleural cavity and intrapleural pressure readings of 0,  $\pm 2$  cm.\* obtained. Closed intercostal siphon drainage was immediately begun; considerable amounts of pus and air gushed out, and respiratory relief immediately followed. *Staphylococcus aureus* was cultured from the pus. Pneumothorax did not recur.

Although sulfadiazine therapy was continued, fever and mild dyspnea, due to the underlying pneumonic process, continued for some time, and one episode of otitis media occurred. Rib resection and open drainage was instituted on April 16, 1942. A total of 65 c.c. of staphylococcal antiserum was given over a period of several days, and skin tests done with staphylococcus carbohydrate were definitely positive by April 7, 1942. The baby was discharged after an eleven-week hospital stay, in good general condition, but with the bronchopleural fistula still open.

CASE 2.—R. M., a 5-month-old white male, was admitted on Jan. 30, 1942, with a history of fever and rapid grunting respirations for the preceding four days. On the day of entry, the dyspnea became much worse and two generalized convulsions occurred. At the time of admission his temperature was  $40.5^{\circ}$  C., and he was pale, prostrated, and extremely dyspneic. The abdomen was quite distended. Movement of the right chest was limited, and

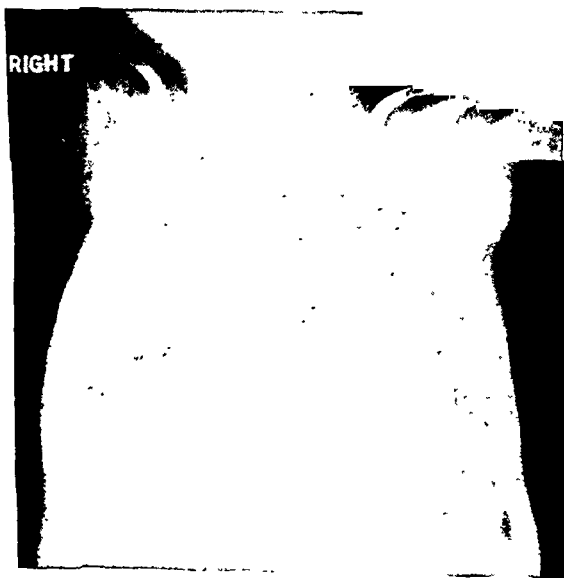


Fig. 5.

there was dullness to percussion over the entire right lung. Tubular breath sounds were heard over the superior portion of the right chest; inferiorly, the breath sounds were suppressed. The chest roentgenogram (Fig. 5) presents the picture of empyema with some shift of the mediastinum, but in addition there are several clear areas to be seen—that is, a pyopneumothorax. Thoracentesis yielded 10 c.c. of thick fluid (positive for *Staph.*

\*These and subsequent intrapleural pressure readings refer to centimeters of water, the pressure at the end of inspiration preceding that at the end of expiration.

*aureus*) and 10 c.c. of air under pressure. Shortly afterward, while a lumbar puncture was being done, the baby went into a state of collapse, the skin became mottled, and respiration practically ceased. Fluoroscopic examination demonstrated a massive right pneumothorax with considerable mediastinal shift. Thoracentesis now produced 80 c.c. of pus and air; an intercostal tube was inserted, and marked relief of symptoms occurred. Closed siphon drainage was maintained until Feb. 16, 1942, when a rib resection was done. Additional treatment consisted of sulfadiazine and supportive measures.

The baby's temperature remained elevated for the first two weeks, but his hospital course was quite favorable, and he was discharged after a stay of eight weeks with the bronchopleural fistula closed.

CASE 3.—S. S., a 4-month-old white female, was admitted on Jan. 5, 1943. She had been hospitalized elsewhere since Dec. 26, 1942, with the diagnosis of pneumonia. Despite sulfadiazine medication, her symptoms had continued, and she had developed a pleural effusion from which the *Staph. aureus* was cultured. On Jan. 2, 1943, fluid and air were removed from the right pleural cavity. On admission to the St. Louis Children's Hospital her temperature was 38° C.; she was acutely ill, quite cyanotic and coughing constantly, and there was cellulitis of the right chest wall. There were a flat percussion note and diminished breath sounds over the entire right lung field.

Cyanosis continued despite therapy with oxygen and sulfapyrazine. She remained in a very critical condition, and her respiratory difficulty and cyanosis gradually increased to the point where she was moribund. On the second hospital day a thoracotomy was done with the release of 100 c.c. of pus and air under great tension, and closed siphon drainage was instituted. Immediate and marked relief resulted from this procedure, and her general condition at once began to improve. Open drainage was instituted on Jan. 18, 1943. She was discharged after a hospital stay of four weeks in good general condition and with the chest wound healed.



Fig. 6.

CASE 4.—F. M., a 9-year-old white male, was admitted on Aug. 2, 1943. During the preceding month he had been successfully treated at another hospital for mastoiditis, lateral sinus phlebitis, and meningitis due to the *Bacillus proteus*. Shortly before he was transferred to the St. Louis Children's Hospital, he had a recurrence of fever, and signs of pneumonia developed in the left chest. A pleural effusion developed, and 400 c.c. of purulent fluid were obtained from the left pleural cavity. Culture of this fluid revealed *Staph. aureus*.

On admission his temperature was 38.5° C. He appeared chronically ill, apprehensive, and markedly dyspneic, and used his accessory respiratory muscles to the fullest degree. The breath sounds were diminished over the entire left lung field, but except for some percussion dullness at the left base, the remainder of the left chest was hyperresonant. The intrapleural pressure readings were 0, +12 cm. Closed intercostal siphon drainage was begun. A chest roentgenogram the following day (Fig. 6) shows the character of the pyopneumothorax in this patient. It should be noted that the process is bilateral. Obviously, the drainage tube was not functioning properly, so it was reinserted in a higher interspace with the release of a large amount of pus and air from the chest, and for the first time a definite improvement in respiratory symptoms was noted. On the third hospital day a thoracentesis on the right produced a few cubic centimeters of pus, and closed intercostal drainage was also begun on that side. *Staph. aureus* was cultured from the pleural fluid. Once surgical drainage was well established, his general condition began to improve. Additional therapy consisted of sulfapyrazine and blood transfusions. Open drainage was begun on Aug. 12, 1943, and by Sept. 9, 1943, both thoracotomy sites were healed. At the time of discharge on Oct. 30, 1943, both lungs appeared normal on fluoroscopic examination; he was gaining weight and was in good general condition.

CASE 5.—J. O., a 5-month-old white female, was admitted on July 19, 1940, with a history of having had an upper respiratory infection for four days, followed on the second day by rapid grunting respirations. Her admission temperature was 39.5° C.; she was acutely ill, quite dyspneic, and mildly cyanotic. The entire right chest exhibited percussion dullness and diminished breath sounds to physical examination, and diffuse haziness on fluoroscopy. Therapy with sulfathiazole was begun, and the baby improved slightly during



Fig. 7.

the first three hospital days. However, on the third hospital day, a roentgenogram revealed definite evidence of fluid and air in the chest (Fig. 7) and a slight shift of the mediastinum. A few cubic centimeters of thick pus, from which *Staph. aureus* was cultured, were obtained on thoracentesis. Intercostal drainage done that same day produced considerable air and pus. Closed siphon drainage was converted to open drainage after two days. A definite bronchopleural fistula developed, and the baby's course was quite stormy

for the first ten days. However, she gradually improved; the tube was finally removed, and she was sent home after a five week hospital stay with a small pleural sinus still present.

She remained well for about a week but then became irritable and began to breathe with noticeable effort. She would lie only on her right side and had recurrent episodes of respiratory distress. On re-entry into the hospital on Sept. 11, 1940, her temperature was normal, and she presented the picture of massive pneumothorax: dyspnea, cyanosis, shift

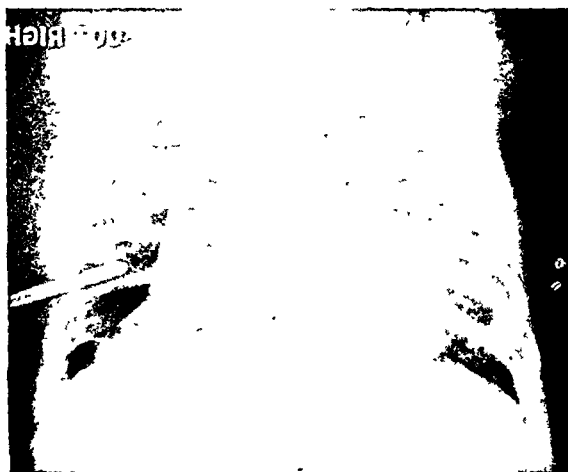


Fig. 8.

of heart and trachea to the left, tympany and diminished breath sounds over the right chest. A needle was immediately inserted into the right pleural cavity and intrapleural pressure readings of +15, +30 cm. obtained. After removal of 800 c.c. of air, the pressures had fallen to -5, +5 cm., and she was considerably relieved. The intrapleural tension rapidly mounted again, however, so closed intercostal siphon drainage was instituted, and large amounts of air bubbled forth constantly from the chest. On the fourth hospital day, she had a recurrence of symptoms, which were relieved promptly by adjusting the tube. A roentgenogram taken at that time is shown in Fig. 8. The picture resembles very closely that seen on fluoroscopy at the time of entry. Very little drainage of pus occurred during this hospital admission. The closed system of drainage was converted to an open one after seventeen days; the bronchopleural fistula gradually closed, and she was discharged home well on Oct. 13, 1940.

These five patients illustrate well the nature of tension pyopneumothorax in children: the rapid onset, the alarming symptoms produced (which often completely overshadow the effects of the staphylococcal infection itself), and the prompt satisfactory response to closed intercostal siphon drainage. The rapidity with which treatment was carried out was life-saving in the first two patients. In the third, treatment was unnecessarily delayed. From her appearance at the time thoracotomy was finally carried out, she certainly could not have survived much longer.

Although pneumothorax was most pronounced in the fourth and fifth patients, it occurred more gradually, and therapy could be carried out with more deliberation, yet their respiratory embarrassment was profound and might well in time have ended fatally. It should be pointed out that the fourth patient was an older child and that he tolerated respiratory difficulties of a degree

that no small infant could. The fifth patient suffered two episodes of pyopneumothorax; pus predominated on the first occasion and air on the second. Respiratory embarrassment was definitely greater on the latter occasion.

There should be no hesitancy about the carrying out of a thoracentesis or a simple thoracotomy for intercostal drainage in patients with tension pyopneumothorax. They are relatively minor procedures which can be done at the patient's bedside without the benefit of elaborate apparatus. No patient's condition should ever be regarded as being sufficiently critical to interdict these live-saving procedures.

CASE 6.—D. H., a 10-month-old white male, was admitted on Dec. 31, 1936, with the history of an upper respiratory infection for the preceding six days. For the last three days there had also been fever and mild dyspnea, and on the morning of admission the child suddenly became cyanotic and extremely dyspneic. The temperature was 39.5° C. on admission; the general picture was that of a cyanotic, critically ill child whose respiratory excursions were limited but who seemed to fight for every breath and was rapidly becoming exhausted. The interspaces on the right were full; the percussion note was tympanitic and the breath sounds greatly depressed over the entire right chest. The breath sounds were of tubular quality on the left. The chest roentgenogram (Fig. 9) shows the extensive right pneumothorax with marked displacement of the mediastinum and an infiltration in the upper right lung field.



Fig. 9.

Thoracentesis was immediately done. The intrapleural pressure readings were +4, +8 cm., and 300 c.c. of air were easily withdrawn from the right pleural cavity. The patient experienced only temporary relief from this procedure, and the mediastinum remained in its former position, thus indicating that a bronchopleural fistula was present of sufficient size to allow air to enter the pleural cavity rapidly. Closed intercostal siphon drainage was then done, and considerable air bubbled forth from the chest. The child expired an hour later.

At autopsy the right pleural cavity contained 100 c.c. of thin, light greenish fluid from which *Staph. aureus* was cultured. The right upper lobe was congested and was fixed to the

chest wall by a thick layer of fibrinopurulent exudate. It contained four abscesses ranging from 1 to 3 mm. in diameter, the largest of which was connected with the pleural space by a sinus tract approximately 1 mm. in diameter. The right middle and lower lobes were congested and atelectatic. In microscopic section the pleura was covered with a fibrinopurulent exudate, and the sinus tract extending from the pleura into the lung abscess could be identified. The smaller bronchioles were filled with polymorphonuclear leukocytes, and there were scattered foci of alveolar consolidation throughout the upper lobe. The left lung showed changes which were interpreted as evidence of early aspiration pneumonia.

CASE 7.—R. S., a 4-week-old white female, was admitted on June 20, 1938. Two days prior to admission she had become irritable and feverish and had begun to vomit. Her abdomen became distended, and she seemed to suffer some abdominal pain, which was relieved by an enema. On the day of admission, she began to have spells of dyspnea and cyanosis which rapidly increased in severity.

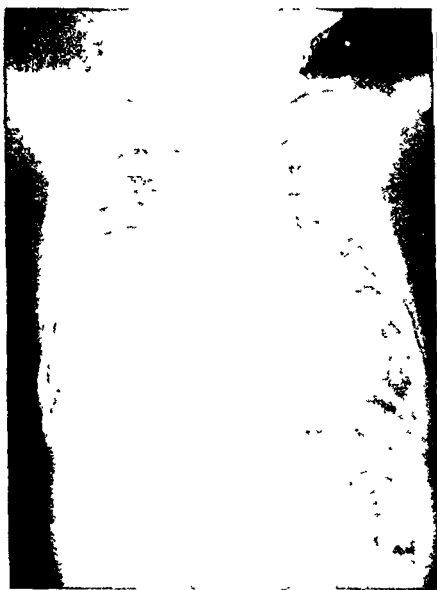


Fig. 10.

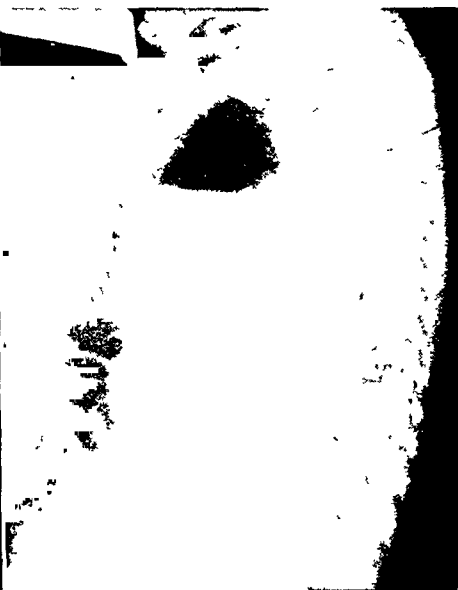


Fig. 11.

On admission her temperature was 36.6° C.; she was moribund, cyanotic, and dyspneic. The right side of the chest exhibited fullness of the interspaces and limited respiratory excursions; there was inspiratory retraction of the suprasternal space and of the interspaces on the left. The percussion note over the right posterior chest was flat, and breath sounds were absent over the entire right chest. The abdomen was distended, and the liver edge was felt 4 cm. below the costal margin. The chest roentgenograms (Figs. 10 and 11) show the extensive pyopneumothorax with shift of the mediastinum to the left.

Thoracentesis was immediately performed, and 20 c.c. of pus were withdrawn along with a considerable amount of air under pressure. *Staph. aureus* was cultured from the pus and from the blood culture. The baby experienced some relief from the thoracentesis, and with the help of an oxygen tent her color became normal. Four hours after admission closed intercostal siphon drainage was instituted with return of at least 60 c.c. of thin purulent material and a considerable amount of air. Air continued to bubble forth from the pleural cavity, and the baby did quite well for the first two hospital days. She then began to lose ground, became listless, refused to take feedings, and developed a high fever. Despite continued oxygen and the liberal use of parenteral fluids she expired on the fifth hospital day.

At autopsy there was a thick white fibrinous exudate over the entire right lung, but there were no adhesions between the two pleural surfaces on that side and only a few cubic centimeters of pus in the right pleural cavity. There was a confluent bronchopneumonia of the entire right lung and of the left lower lobe. In the right lung there were two abscess cavities, 1 to 2 cm. in diameter, which had ruptured into the right pleural space. One of these opened onto the diaphragmatic surface of the right lung, and the pus which had escaped from it was completely encapsulated; the other communicated with the open pleural cavity through a jagged opening several millimeters in size. In microscopic section there was extensive consolidation with red cells and mononuclear cells, and numerous clumps of cocci could be seen. Polymorphonuclear cells were not abundant. Except for a large fatty liver, the other post-mortem findings were irrelevant.

CASE 8.— D. Y., a 7-week-old white female was admitted on Dec. 21, 1940. She had been ill for three days with symptoms of fever, slight cyanosis, and dyspnea.

Her admission temperature was 38.0° C.; she appeared critically ill and exhibited rapid shallow respirations, cyanosis, and pallor. The entire right chest was hyperresonant to percussion, and the breath sounds were scarcely audible. A chest roentgenogram revealed several large cystlike areas in the right lung field (Fig. 12).



Fig. 12.

She was given oxygen, which greatly relieved her cyanosis and dyspnea, and sulfathiazole therapy was begun. The following morning a thoracentesis was done and intrapleural pressure readings of 0, +7 cm. obtained. One hundred c.c. of air together with a few cubic centimeters of pus were aspirated. *Staph. aureus* was cultured from the pus. Closed siphon drainage of the chest was immediately begun with resultant improvement in breathing, but she soon became worse, developed hyperpyrexia, and expired the next day.

At autopsy the right pleural surfaces were covered with a thick fibrinopurulent exudate. The right lung contained multiple abscess cavities, one of which communicated with a bronchus and with the pleural cavity by means of a sinus tract about 7 mm. in diameter. Two additional abscesses communicated with the pleura by small sinus tracts, but no bronchial communication could be demonstrated for these. The left upper lobe was covered by a small amount of fibrinopurulent exudate, and there were several foci in the lobe interpreted as early abscesses. There were focal necroses in the liver.



These three cases represent instances in which tension pyopneumothorax produced alarming symptoms; treatment in each case was prompt and effective from the standpoint of the pneumothorax, death coming as a result of the overwhelming toxemia of the infection. The post-mortem findings of multiple abscesses and massive consolidation of the lung indicate the severe nature of the pneumonic process. If penicillin had been available, the latter two of these three children might have recovered.

CASE 9.—J. O., a 3-week-old white female, was admitted on March 10, 1939, after an illness of two days, which began with rhinitis and cough, followed the next day by fever, listlessness, and anorexia. During the preceding week a few small furuncles had been noted on the scalp.

Her admission temperature was 39.2° C.; she was moderately ill and exhibited mild dyspnea, but there was no cyanosis. The lungs were clear to percussion and auscultation, but on fluoroscopy the right middle lobe was seen to be consolidated.



Fig. 13.

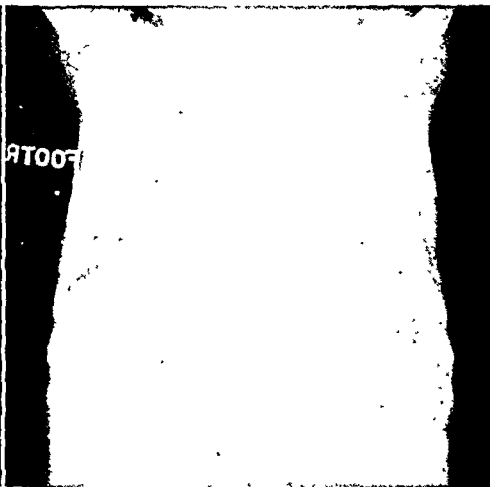


Fig. 14.

The baby was given sulfapyridine and parenteral fluids, but rapidly became worse, and by the next day dyspnea and cyanosis were sufficient to require oxygen therapy. The chest roentgenogram now showed a definite pleural effusion on the right (Fig. 13). By the third hospital day the patient had developed extreme dyspnea, and continued to present symptoms of toxemia despite the fact that her temperature had become normal. The chest roentgenogram at this time (Fig. 14) revealed an extension of the pleural effusion in which there were several small areas of decreased density. On this day she had a sudden episode of apnea and cyanosis, and was revived with considerable difficulty. A similar episode recurred later that day, and because the symptoms were thought to be due to possible brain involvement, a lumbar puncture was done and normal spinal fluid obtained. The right intercostal spaces were noted to be bulging, and on fluoroscopy of the chest an extensive right pneumothorax was discovered, involving about a third of the lung field. Thoracentesis was immediately carried out, but only 7 c.c. of pus and 10 c.c. of air were obtained. *Staph. aureus* was cultured from this pus. The patient expired shortly afterward, just as preparations were being made for surgical drainage. Permission for autopsy was not obtained.

CASE 10.—W. P., a 1-month-old white male, was admitted on Oct. 12, 1939. He had been well until the previous evening, at which time he began to grunt with each respiration

and to cough occasionally. Neither the parents nor the doctor who saw him were particularly concerned about him until three hours before admission. At this time he suddenly threw his head backwards, gasped for breath, and became cyanotic. He sustained two subsequent attacks of a similar nature before admission to the hospital.

On admission his temperature was  $38.8^{\circ}$  C. He seemed alert and fairly vigorous but was deeply cyanotic and moderately dyspneic. The interspaces of the right chest were full, and on that side the percussion note was tympanitic and the breath sounds distant and suppressed. A chest roentgenogram (Fig. 15) revealed a large pneumothorax on the right and an infiltration in the left upper lobe.

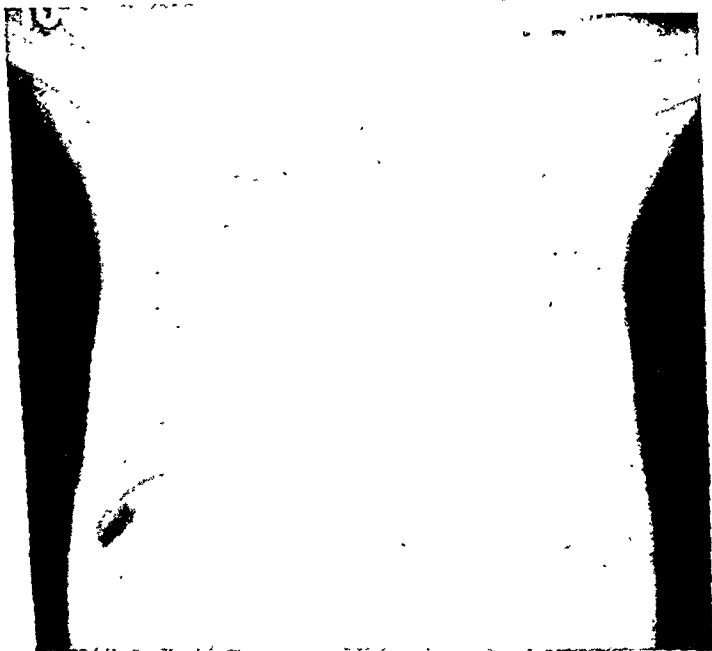


Fig. 15.

The patient was considered to have a spontaneous pneumothorax and was placed in an oxygen tent which gave him considerable relief. Sulfapyridine therapy was begun, and several blood transfusions were given during the next few days. He continued to do fairly well, exhibiting very little fever, until the fifth hospital day. At this time his respiratory rate increased markedly, and evidence of fluid in the right pleural cavity was noticed on fluoroscopic examination. Thirty cubic centimeters of pus (under pressure) were aspirated from the right chest, from which was cultured *Staph. aureus*. Subsequent thoracenteses yielded pus and air, and on the eighth hospital day continuous closed intercostal drainage of the right chest was begun. In spite of these procedures the patient died that same day.

At autopsy the right pleural cavity contained three separate empyema pockets, and there was a fibrinous pericarditis. There was an abscess, 1 cm. in diameter, in the right middle lobe through which there was a sinus tract 1.5 mm. in diameter extending from the pleural cavity to a small bronchus. Microscopic sections revealed an extensive consolidation with mononuclear cells, polymorphonuclear leukocytes, and desquamated epithelial cells enmeshed in organizing fibrin. The bronchioles contained plugs of fibrin and degenerated leukocytes. The pleura was considerably thickened.

These two cases represent the effects of pyopneumothorax in their severest form. In the first, the tension pneumothorax was the immediate cause of death; had thoracentesis been done sooner and had more air been withdrawn from the

chest, the outcome might have been different. In the second, thoracentesis was unfortunately postponed as was surgical drainage, and the pneumothorax contributed appreciably to the fatal outcome.

### MORTALITY

Of the forty-two cases in this series, eleven patients died—a case fatality rate of 26.2 per cent. Table III illustrates the experiences of others, as compiled from the literature. Only those reports were included which represented a continued experience with this disease at a given clinic over a number of years. No attempt was made to analyze the method of therapy employed.

TABLE III. MORTALITY FROM STAPHYLOCOCCAL EMPYEMA

AUTHOR	CHILDREN OF ALL AGES			CHILDREN UNDER 1 YEAR OF AGE			CHILDREN UNDER 6 MONTHS OF AGE		
	CASES	DEATHS	PER CENT	CASES	DEATHS	PER CENT	CASES	DEATHS	PER CENT
Ladd and Swan <sup>14</sup>	33	9	27.3	22	8	36.3	12	8	66.7
Riley <sup>11</sup>	29	10	34.5	22	8	50.0	14	5	35.7
Hochberg and Kramer <sup>5</sup>	33	13	40.0	14	7	52.5	11	6	54.5
Neuhof and Berck <sup>6</sup>	31	13	42.0	15	8	66.7			
McEnery and Brennemann <sup>4</sup>	14	6	42.8	6	4	50.0			
Spence <sup>1</sup>	32	14	44.0	10	5				
Hurwitz and Stephens <sup>8</sup>	8	3	37.5						
Farr and Levine <sup>18</sup>	6	4	66.7						
Total	186	72	38.7	89	40	45.0	37	19	51.3
St. Louis Children's Hospital	42	11	26.2	27	11	40.7	20	7	35.0

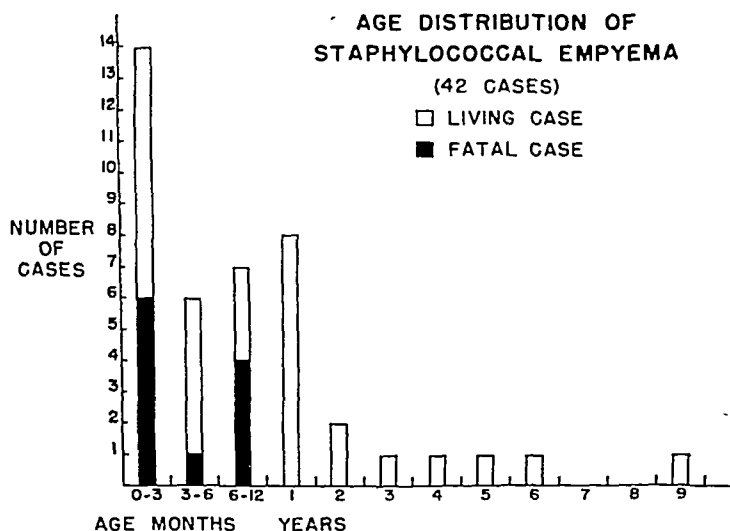


Fig. 16.

It is at once apparent that a factor of great importance in the mortality is the age of the patient. Staphylococcal empyema is not only more common in young infants, but it is also more serious. In our series the case fatality rate as related to age is shown in Fig. 16. In the fourteen infants under 3

TABLE IV. MORTALITY FROM STAPHYLOCOCCAL EMPYEMA BY YEARS

YEAR	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	TOTAL
Total cases	3	2	1	2	2	4	12	2	10	4	42
Deaths	2	1	1	1	1	2	2	0	1	0	11
Mortality rate	60%					15.6%					26.2%
Children under 1 year	2	1	1	1	1	2	8	2	6	3	27
Deaths	2	1	1	1	1	2	2	0	1	0	11
Mortality rate	100%					23.8%					40.7%

months of age, 42.8 per cent died; of the six between 3 and 6 months of age, 16.7 per cent died; between 6 and 12 months of age, 57.1 per cent of the seven infants died, and of the fifteen 1 year or older there were no fatalities.

Table IV presents an analysis on a yearly basis for our series of cases, the entire series being represented in the upper portion of the table, and those cases under 1 year of age in the lower portion.

The division of cases into two five-year periods was not made solely to divide the entire period covered by the series into two equal portions, for in 1939, sulfapyridine, a drug considerably more effective than sulfanilamide against the staphylococcus, came into wide usage. It is seen that whereas the total mortality rate for the first five-year period is 60 per cent, that of the second has been reduced to 15.6 per cent. A similar reduction in mortality in recent years was noted by Riley.<sup>11</sup> In our series it is due to several factors: an increase in the number of cases in recent years has made the house staff more experienced in the diagnosis and general handling of these patients; the more frequent use of the fluoroscope in the examination of infants' chests has led to earlier and more nearly accurate diagnosis; and the importance and dangers of pyopneumothorax have become more widely appreciated. Further, the conclusion that the sulfonamide drugs, given to most of the patients during the latter five-year period, were a definite factor in lowering the mortality cannot be lightly dismissed. Intercurrent streptococcal and pneumococcal infections, so likely to occur in any children's hospital, have certainly been better controlled since the advent of sulfonamide chemotherapy. This factor, together with the known antistaphylococcal effect of the sulfonamide drugs, however small it may be, undoubtedly was a real help to our patients. The general improvement in diagnostic methods can be strikingly illustrated by a comparison of Rienhoff and Davison's<sup>19</sup> series, covering the period from 1889 to 1927, with our own. In the former, twenty of eighty cases, or 25 per cent, were first diagnosed at autopsy while in our series only two of forty-two cases (5 per cent) were unrecognized during life. That this reduction of mortality in our series in recent years is not due to a fortuitous age distribution is borne out in the lower portion of Table IV in which only those cases under one year of age are considered. The same favorable trend is illustrated: a reduction from 100 per cent mortality in the years 1934 to 1938, to 23.8 per cent in the last five years.

Contrary to the statements of Ladd and Swan,<sup>14</sup> we believe that bacteriemia does influence the outcome in cases of staphylococcal empyema. Positive blood

cultures were obtained in thirteen of the thirty-four patients for whom blood cultures are recorded. Six of these thirteen patients, or 46.1 per cent, died as contrasted to a fatality rate of 23.8 per cent for the 21 nonbacteriemic cases.

The principal causes of death in the eleven fatalities which occurred in our series are as follows: Seven patients died of toxemia; in one of these tension pneumothorax was also a major factor; in another the empyema was bilateral and bacteriemic was present. One patient succumbed to a tension pneumothorax. One patient died suddenly following open drainage of the chest; the cause of death here is not known; air embolism and open pneumothorax secondary to open drainage of the chest are two definite possibilities. In two patients, empyema was unrecognized until a postmortem thoracentesis was performed.

#### TREATMENT

A consideration of these factors points the way toward a logical plan of therapy for infants with staphylococcal empyema.

First, therapy should be directed against the infecting agent. The fulminating course of the disease in some patients may produce death before empyema becomes clinically evident and can be approached surgically. This was the case in two of our patients, the empyema cavity being quite small on post-mortem thoracentesis. If it is possible to treat the patient at the stage in which the pneumonia is still of the hemorrhagic variety and before definite abscesses have formed, the results should be distinctly better, and occasionally an empyema might be aborted. Once lung abscesses are formed, all forms of therapy become much less effective. Of the three agents which are of value in combating the staphylococcus (penicillin, the sulfonamide drugs, and anti-staphylococcal serum), penicillin is to be preferred because it has proved itself to be much more powerful than the latter two. At the present time it is our policy to administer penicillin subcutaneously in amounts of 5,000 to 10,000 units every two hours to any small infant with pneumonia who demonstrates one of the following phenomena: (1) failure of response to one of the sulfonamide drugs (exclusive of sulfanilamide) in adequate dosage over a period of twenty-four to forty-eight hours, (2) presence of staphylococcal bacteriemia, (3) a massive pneumonic shadow involving all or the majority of one side of the chest, (4) the occurrence of spontaneous pneumothorax. As the recent experiences of Philips and Kramer<sup>20</sup> indicate, had penicillin been available throughout the period covered by this study, the mortality would most certainly have been lower, and the total duration of the illness shorter.

There are four patients in our series who we feel were definitely benefited by the use of sulfonamide chemotherapy. Definite temperature responses occurred in all four, and they showed a clinical response of moderate degree. Sulfadiazine was employed in two of the cases, sulfathiazole in one, and sulfapyrazine in one. Antistaphylococcal serum was also used in one of these but was given relatively late in the course of the disease at a time when some improvement was already manifest. Striking clinical improvement did not

occur in any case, however, until thoracentesis was done, and eventual cure was effected in each case by thoracentesis alone.

Our conviction that the sulfonamide drugs are occasionally of some value in staphylococcal lung infections is strengthened by the following case, an instance of staphylococcal pneumonia without empyema, in which the patient recovered completely on sulfathiazole medication. This case is not included in the series herein reported because empyema did not develop. The patient, an 8-month-old white female, was admitted to the hospital after an illness of three days and presented typical findings of lobar pneumonia. Sputum and blood cultures were positive for *Staph. aureus*. On sulfathiazole medication the temperature fell by lysis to normal in six days; at that time resolution of the lung shadow was first noted, and the baby showed definite clinical improvement. She was discharged well on the fourteenth hospital day, having shown no evidence of empyema at any time.

From such experiences we feel that sulfonamide chemotherapy does have a definite though quite limited place in the treatment of staphylococcal infections of the lung in children. Of the thirty-four patients in our series who were given one of the sulfonamide drugs, the four mentioned are the only ones, however, in which a clear-cut effect on the staphylococcal infection from such treatment was observed. In the others, symptoms progressed rapidly, and real improvement did not occur until surgical drainage was established.

Antistaphylococcal serum was employed in four patients. The results in this series are largely inconclusive: Two of the patients had extremely prolonged febrile courses following surgical drainage, and the relative role of serum in bringing about eventual recovery may have been appreciable but is impossible to evaluate. One of the other patients was mentioned in the discussion of chemotherapy; the remaining case was that of a small infant who was extremely toxemic and exhibited no fever, and here, too, the effect from serum was inconclusive. All of these patients recovered, but two of them were over one year of age and, therefore, in that group in which the mortality is lowest. From our over-all experience with staphylococcal infection, however, we believe that antistaphylococcal serum might well be beneficial in the small infant (i.e., one whose immune responses might not be adequate) whose course seems unnecessarily prolonged.

Second, general supportive measures are of the greatest importance. The great majority of the patients in this series received one or more blood transfusions. Oxygen was used freely to combat marked dyspnea, cyanosis, and excessive abdominal distention. Parenteral fluids were used frequently to relieve dehydration and to provide food in the form of dextrose, Amigen, and plasma. Once surgical drainage has been established, considerable amounts of protein may be lost from the patient's body through drainage of pus.

Third, surgical drainage is paramount. Symptoms and signs of infection in patients with staphylococcal empyema usually persist until the empyema is drained, whereupon a veritable "crisis" occurs: The temperature and white blood count drop to normal, the patient looks much better, his appetite and

color improve, dyspnea disappears, and oxygen therapy is less often needed. Because of the pathogenesis of staphylococcal empyema, we believe that certain principles are of the greatest importance from the surgical viewpoint: The foremost of these is the avoidance of tension pneumothorax. First, consider every pneumothorax in a young baby to be the result of staphylococcal pulmonary disease until proved otherwise. Second, a diagnostic thoracentesis should be done in every case of pneumonia in which signs of infection persist despite adequate antibiotic or chemotherapy. Third, once the diagnosis of a staphylococcal empyema involving the greater portion or all of that particular pleural space has been established, surgical drainage should be done immediately. Closed intercostal siphon drainage is the method of choice; the procedure is easily and quickly accomplished, is easily withstood by even the most toxemic patient, permits adequate drainage, and, most important of all, obviates the possibility of tension pneumothorax. After a suitable length of time and upon stabilization of the mediastinum, this is converted to open drainage. If a tension pyopneumothorax is present at the time the patient is first seen, thoracentesis should be done with withdrawal of all available air, to be followed immediately by closed siphon drainage to prevent recurrence.

If the empyema proves to be more or less localized by preformed pleural adhesions and is not extensive, then surgical drainage is not as urgent, for if a pyopneumothorax does form, it will often be limited in extent and unable to constitute a threat to the patient's life. The time for and the type of surgical drainage is left to the discretion of the thoracic surgeon in such cases. However, the danger of pyopneumothorax is such a constant one that during the preoperative course the patient should be constantly watched, and a thoracentesis set made immediately available at all times.

No attempt has been made in this series to analyze the type of surgical drainage, for it varied with the status of each patient's particular empyemic process and was highly individualized. While four of our patients recovered by thoracentesis alone, these were the ones whose empyemic processes were limited in extent and in whom the sulfonamide drugs seemed to exhibit a definite beneficial effect. In several patients, in whom empyema had been present for several days before hospitalization and in whom the intrapleural pus was quite thick and tenacious, rib resection and open drainage were done on admission to the hospital, for it was obvious that an intercostal drain would not have provided an adequate outlet for the infected effusion.

Despite the hope that the use of intrapleural and parenteral penicillin might obviate the necessity for surgical drainage in the treatment of empyema—a hope which has been expressed frequently in the recent medical literature—we are convinced that surgical drainage is, and will continue to be, a principle of fundamental importance in the management of patients with staphylococcal empyema. Poppe<sup>21</sup> and Blades and associates<sup>22</sup> point out that even though an empyema cavity may be rendered sterile by intensive penicillin therapy, surgical drainage must still be used to effect eventual cure in the majority of patients.

## SUMMARY AND CONCLUSIONS

1. Forty-two cases of staphylococcal empyema observed at the St. Louis Children's Hospital during the past ten years are presented and discussed. The mortality rate for this series, which does not include penicillin-treated cases, is 26.2 per cent.

2. The importance of pyopneumothorax and the frequency with which it occurs are emphasized. This complication occurred in seventeen (40.5 per cent) of our patients; it was a direct cause of death in one patient and contributed in large part to the death of another. Four additional patients experienced alarming symptoms and would have died without prompt and correct treatment. Staphylococcal pyopneumothorax should be seriously considered in the differential diagnosis of spontaneous pneumothorax in young infants.

3. The striking predilection of staphylococcal empyema for young infants and the higher mortality in this group are demonstrated.

4. General supportive measures and surgical drainage constituted the two most important aspects in successful treatment in our series. The use of closed intercostal siphon drainage is advocated as a means of obviating the possibility of tension pyopneumothorax and at the same time providing adequate drainage. The sulfonamide drugs and antistaphylococcal serum were of limited usefulness.

## REFERENCES

1. Spence, R. C.: *Am. J. Dis. Child.* 20: 545, 1920.
2. McNeil, C., Macgregor, A. R., and Alexander, W. A.: *Arch. Dis. Childhood* 4: 270, 1929.
3. McEachern, J. D.: *Brit. J. Surg.* 20: 653, 1933.
4. McEnery, E. T., and Brennemann, J.: *The Pleura*, In Brennemann's *Practice of Pediatrics*, Hagerstown, Md., 1944, W. F. Prior Company, Inc., vol. 2, chap. 53.
5. Hochberg, L. A., and Kramer, B.: *Am. J. Dis. Child.* 57: 1310, 1939.
6. Neuhof, H., and Berek, M.: *Arch. Surg.* 30: 543, 1935.
7. Benson, C. D., and Penberthy, G. C.: *Ann. Surg.* 113: 1082, 1941.
8. Hurwitz, S., and Stephens, H. B.: *J. PEDIAT.* 14: 11, 1939.
9. Lanman, T. H., and Dimmler, C. L.: *Am. J. Surg.* 54: 29, 1941.
10. Ellenberg, S. L., and Martin, A. T.: *New York State J. Med.* 42: 1243, 1943.
11. Riley, C. M.: *J. PEDIAT.* 24: 577, 1944.
12. Macgregor, A. R.: *Arch. Dis. Childhood* 11: 195, 1936.
13. Kanof, A., Kramer, B., and Carnes, M.: *J. PEDIAT.* 14: 712, 1939.
14. Ladd, W. E., and Swan, H.: *J. PEDIAT.* 23: 297, 1943.
15. Clemens, H. H., and Weens, H. S.: *J. PEDIAT.* 20: 281, 1942.
16. Johnson, F. E.: *Am. J. Dis. Child.* 33: 740, 1927.
17. Cohen, Philip: *M. Clin. North America* 22: 1473, 1938.
18. Farr, C. E., and Levine, M. I.: *Surg., Gynec. & Obst.* 46: 79, 1928.
19. Rienhoff, W. F., and Davison, W. C.: *Arch. Surg.* 17: 676, 1928.
20. Philips, B., and Kramer, B.: *J. PEDIAT.* 26: 481, 1945.
21. Poppe, J. Karl: *J. A. M. A.* 129: 435, 1945.
22. Blades, B., Hamilton, J. E., and Dugan, D. J.: *Surgery* 17: 572, 1945.



## BILATERAL RENAL AGENESIS

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AMONG approximately 5,000 necropsies on fetuses and newborn infants performed at the Chicago Lying-in Hospital\* during the last ten years, 20 infants with complete renal agenesis have been observed. Nine were born in this hospital, six were born at home or in other hospitals, and were sent here for post-mortem examination. Five were examined grossly in other hospitals or mortuaries, and tissues and histories sent here for study. The incidence in the total series of autopsies is 4 per 1,000 dead infants and fetuses. The incidence among deliveries in this hospital is approximately 0.3 per 1,000 births or 7.0 per thousand deaths and stillbirths. The higher incidence among infants born in this hospital is probably due to the inclusion in the total number of autopsies of a disproportionately large number of infants who died in the antepartum period. Renal agenesis is a much less frequent cause of death in fetuses dying before labor than it is in infants who are born alive or who die during labor. These figures are in sharp contrast to the widely accepted belief that complete renal agenesis is a rare condition almost never found except in grossly monstrous infants.

Several reviews have appeared in the last few years in which each author has discussed the cases previously described by other investigators and has added one or two he has personally observed. Rosenbaum,<sup>1</sup> in 1931, combined 32 cases which had been found in the literature by Coen and reported in 1884, with 59 which were subsequently described by other authors and added one of his own. Madison,<sup>2</sup> in 1934, reported 4 cases of his own and found 6 more that had been observed by other investigators. In 1937, Amolsch<sup>3</sup> read all of the previous reports and added 4 more cases bringing the total to 119. In 1939, Soloway<sup>4</sup> reported 2 cases, the only ones observed in the course of 12,000 autopsies at the Cook County Hospital.

In 1940, Hinman<sup>5</sup> was able to find 18 other recorded cases. After adding one of his own, he concluded that 135 authentic cases had been described since 1663. Later that same year Grimm<sup>6</sup> reported the case of another infant which was unusual in contrast to most of those previously reported, in that the absence of kidneys and ureters was the only abnormality. In 1944, Nation<sup>7</sup> reported 3 similar infants found among 27,000 autopsies at the Los Angeles County Hospital. Stokes,<sup>8</sup> also in 1944, described an infant with renal agenesis and multiple internal anomalies.

Among the 119 cases collected by Amolsch in which the descriptions were adequate, there were 81 infants with gross anomalies of the lower limbs. Of these 30 were sirenomelus, 2 apus, 8 monopus, 9 headless monsters with abnormal lower extremities, and 32 exhibited less spectacular disturbances of the lower

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\*Only about one-fifth of these infants were born in the Chicago Lying-in Hospital. The remainder were sent to us for study by the courtesy of many physicians and hospitals in the City through the cooperation of the Chicago Health Department.

limbs. There were 63 males, 24 females, and 32 that were unclassified. Amolsch stated that a dysplasia of the genital system was common in the female and that although the Fallopian tubes were present, the uterus and vagina were ordinarily absent. In 2 cases both adrenal glands were absent and in 4 cases one was absent.

The 20 infants included in the present report exhibit much the same findings as those previously described. The principal difference lies in the proportionally small number who would be considered gross monsters. Four exhibited multiple skeletal abnormalities, but in only one was there the great disturbance in the development of the lower part of the body that results in sirenomelus.

The 19 available maternal histories contain nothing of especial note. Maternal age ranged from 18 to 39 years with the median of 24 years. Nine women were primigravidas; 10 were multigravidas. Two had had previous abortions. Only 2 had had more than 2 preceding pregnancies; one had had 11 children, the other, 7 children and 3 abortions. The method of delivery was unrecorded in 2, spontaneous cephalic 9, breech 6, mid-forceps 1, Cesarean section 1, and craniotomy 1. Nineteen of the mothers were white; 1 was Negro.

An attempt to ascertain the amount of amniotic fluid was disappointing. In no instance was it possible to obtain a definite history of rupture of the amniotic sac. In no case were the membranes ruptured artificially prior to or during labor. In no case was an absence of amniotic fluid mentioned and it seems to have been universally taken for granted that the fluid must have escaped prior to hospital admission. In one instance the physician reported that the infant's body was so unusually dry that he encountered some difficulty in extracting it. There is, therefore, no conclusive evidence concerning the amount of amniotic fluid. The fact, however, that (as far as can be determined) no fluid was observed by any of the obstetricians seems to warrant the conclusion that in the majority of cases it was probably reduced in amount. If more definite information concerning the amniotic fluid had been available it might have been possible to shed some light on the importance of secretion by the fetal kidneys in maintaining a normal volume of amniotic fluid. It can be definitely stated, however, that kidney function is not necessary for the maintenance of intrauterine life.

Fetal death occurred prior to the onset of labor in 1 instance, during labor in 6, and after birth in 13. The length of life varied from 25 minutes, to 11 hours and 15 minutes, with a median of 1 hour and 38 minutes. Weight varied from 700 to 3,000 Gm. with a median of 1,645 Gm. There were 17 male and 3 female infants. This is a more striking tendency toward sex-linking than is found in any other malformation except anencephaly. Over 90 per cent of anencephalic infants are females. Interestingly enough, in spite of the multiplicity of malformations which is found in association with anencephaly, not once has renal agenesis been recorded.

Clinical histories of the infants born alive show nothing remarkable. The majority were cyanotic or breathed with difficulty. In a few, in spite of the fact that the heart continued beating for some time, respiration could not be established.

TABLE I. ASSOCIATED MALFORMATIONS

CASE	MATERNAL AGE (YEARS)	GRAVIDITY	ABORTIONS	METHOD OF DELIVERY	GESTATIONAL AGE AT BIRTH IN WEEKS	LENGTH OF LIFE	CLINICAL CAUSE OF DEATH	SEX	WEIGHT (GRAMS)	LIVING WEIGHT (GRAMS)	LUNG WEIGHT FOR NORMAL INFANT OF SAME SIZE (GRAMS)	FEET AND GENITOURINARY	CARDIAC	ABDOMINAL VISCERA	SCHELETAL AND MISCELLANEOUS
1	23	1	0	Sp. ceph.	40	44" I. C.	Hem.	M	2,700	17.0	52				
2	29	2	1	Sp. ceph.	34	11' 14"	Prem.	M	1,380	19.0	30				
3	22	1	0	Breech	34	2' 15"	Asphyx.	M	1,655	Hyp.	38				
4	33	3	0	Ces.	36	2' 14"	Asphyx.	M	1,980	Hyp.	44				
5	21	2	0	Breech	38	S. B.	Asphyx.	M	1,600	13.3	38				
6	28	3	0	Sp. ceph.	36	1' 38"	Asphyx.	M	3,000	16.6	55				
7	30	8	3	Sp. ceph.	35	S. B.	Asphyx.	M	2,000	Hyp.	44				
8	21	1	0	L. F.	38	3' 8"	Prem.	M	2,330	20.0	47				
9	18	1	0	Sp. ceph.	26	S. B.	Asphyx.	M	700	3.8	20				
10	26	2	0	Sp. ceph.	39	1' 1"	Asphyx.	M	2,150	Extr. hyp.	44				
11	22	1	0	Sp. ceph.	39	1' 32"	Asphyx.	M	1,645	12.5	38				
12	32	12	0	Sp. ceph.	30	S. B.	Asphyx.	M	1,100	13.0	25				
13										Extr. hyp.					
14	22	1	0	Sp. ceph.	28	S. B.	Malf.	M	1,015	16.0	25				

Aortic atresia  
Pulmonary atresia  
Absent rectum and anus  
Hypoplastic adrenals  
Meningocele, microphthalmia  
Hydrocephalus, spina bifida  
Scoliosis, rib anomalies, short neck, absent radii and thumbs, extra toes



The clinical impression as to the cause of death was: intracranial hemorrhage 1, asphyxia 11, and malformation 8. In the 8 with a diagnosis of malformations, there was hydrocephalus (3), multiple skeletal anomalies (4), and a small meningocele (1). In the others, external malformations were absent (6), limited to clubfeet (4), or to those sufficiently mild to be easily overlooked on superficial examination (2). The various malformations are shown in Table I. Clubfeet were found more commonly than any other associated disturbance, but there were 5 infants with gastrointestinal abnormalities (imperforate anus, 4) and 3 with hydrocephalus. Four of the most malformed infants exhibited a somewhat uniform disturbance consisting of contractures of the hips, elbows, and sometimes the knees, with occasional absence or duplication of bones of the extremities and shortening or webbing of the neck. One infant had an almost complete absence of lower extremities. Both this infant and one with generalized contractures of the extremities, had clubhands associated with absence of the thumb and radius.

Two anomalies were observed in almost all of these infants which to my knowledge have not previously been recognized as characteristically associated with renal agenesis. These are hypoplasia of the lungs and an abnormal facial expression.<sup>8</sup>

In the 14 cases with recorded lung weight, this varied from 15 per cent to 60 per cent of the average lung weight for a normal fetus of corresponding size. In the 7 with unrecorded lung weight, all lungs were stated to have been hypoplastic (Table I).

The histologic appearance of all lungs was similar. The bronchi were prominent and proportionately more numerous than normal because of inadequate parenchymatous development. The alveoli were often rudimentary and in many cases they and the respiratory ducts were lined by cuboidal epithelium. Capillary ingrowth into the alveolar walls seemed to have been greatly inhibited. In almost all instances, the lungs resembled those of a fetus of less gestational age than the one in which they were found.

Anencephalic monsters and infants with diaphragmatic hernias frequently show a somewhat similar pulmonary hypoplasia. In many anencephalic infants, especially those with an associated spinal rachischisis, the thoracic cavity is so reduced in size that the lungs do not have room for normal development. An extreme unilateral hypoplasia is usually found in infants with a diaphragmatic hernia. The presence of abdominal viscera within the thoracic cavity reduces the space available for lung growth; both lungs are almost invariably hypoplastic but the reduction in size and in alveolar development is greater in the lung which is on the same side as the diaphragmatic defect.

In infants with renal aplasia the space within the thorax is normal and the hypoplasia cannot be explained on the basis of inadequate room for expansion. There is no apparent relationship between the embryologic development of the lungs and the ureters and kidneys. The reason for delayed differentiation of pulmonary tissue remains unexplained.

The peculiar facies of these infants likewise seems to have no specific embryologic correlation with the renal anomaly. The face most characteristically exhibits an increased space between the eyes, a prominent fold which arises at the inner canthus and sweeps downward and laterally below the eyes, an unusual flattening of the nose, excessive recession of the chin, and moderate enlargement and decreased chondrification of the ears. The face gives a suggestion of premature senility and is sufficiently characteristic to warrant a diagnosis of coexisting renal aplasia when it is observed.



Fig. 1.—Case 2. Lateral view of head showing large low-lying ears.

An interesting associated anomaly which was present in all 3 of the females in this series and which seems to have been present in practically all of those reported in the literature is the complete failure of development of the part of the Müllerian ducts which ordinarily fuse to become the uterus and vagina; the Fallopian tubes are usually normal.

It appears that whatever agent prevents the outgrowth of the ureteral bud from the Wolffian duct inhibits the caudal extension of the Müllerian duct. The Wolffian ducts are not intrinsically altered and in all of the male fetuses in this series, prostate, seminal vesicles, ductus deferens, and testes were normally formed. The Fallopian tubes and gonads in the three females were normal but, instead of being attached to a uterus, the Fallopian tubes ended blindly and became lost in the suprapubic connective tissue.

In the normal 10 mm. embryo, the Wolffian ducts have already given rise to the ureteral buds and the metanephric blastema has condensed around the terminal portion of the growing ureter to initiate the formation of the definitive kidney. Gruenwald<sup>9</sup> has shown that at about this time each Müllerian duct makes its first appearance as a funnel-shaped invagination of the mesonephric ridge. This lies a short distance from the Wolffian duct and is separated from it by mesenchyme. It grows caudad for a very short distance as a separate structure, but soon is found in intimate contact with the wall of the Wolffian

duct, the Müllerian and Wolffian ducts being surrounded by a common basement membrane. Whether the Müllerian duct grows downward beside the Wolffian duct but within its basement membrane, or whether the Müllerian duct comes into existence by being split off from the Wolffian duct has not been definitely determined. At any rate the contact of the two structures is so intimate that inhibition of the normal development of the Wolffian duct necessarily inhibits normal growth of the Müllerian duct. Gruenwald has shown in chick embryos that if downward growth of the Wolffian duct is interrupted, the Müllerian duct will not extend beyond that point. It seems probable, however, that none of



Fig. 2—Case 5. Typical facies. The disk-shaped suprarenal glands are visible in the posterior abdominal cavity.

the infants in this series with bilateral renal agenesis suffered complete interruption in the growth of the Wolffian ducts. It would seem that the inhibition of ureteral outgrowth and of Müllerian tube downgrowth must be a very localized process since all but one of the infants had a bladder and urethra and in the males the Wolffian system was normal except for the absence of ureters and kidneys. Another possible, but highly improbable, explanation consists in

the failure of formation or premature atrophy of the cephalic portion of the Wolffian duct including the portion from which the ureter normally arises. Since the Müllerian duct does not descend caudally in the absence of the Wolffian duct the existing portions of Fallopian tubes may have developed completely from the ostial part of the Müllerian duct which arises from the mesonephric ridge independently of the Wolffian system.

In none of the infants in this series was any portion of ureter present. In none was even rudimentary kidney tissue found in any portion of the abdominal cavity. This finding corroborates the belief of other investigators that the differentiation of the metanephric blastema is dependent on the stimulus afforded by the presence of the ureter.



Fig. 3.—Case 19. Typical facies.

The persistence of the bladder as a slender tubelike structure with little musculature in its wall appears to be secondary to the absence of the stimulation for growth normally found in the necessity for a reservoir for kidney secretions.

The suprarenal glands were normal in all but one infant in this series. In this one instance, the glands were of approximately one-half the normal weight. The component parts showed normal relationships and there was no abnormality except the reduction in size. All of the suprarenal glands in the series were round disklike structures placed flat against the posterior abdominal wall. The usual "cocked-hat" shape of the suprarenal is due to the pressure exerted against it by the upper pole of the kidney. When the pressure is nonexistent it remains undistorted and is a smooth circular flat structure.

#### SUMMARY

Twenty instances of complete renal agenesis have been observed during a ten-year period among approximately 5,000 infants who were subjected to post-mortem examination following intrauterine death or death in the neonatal period.

There was no relation to maternal age or parity, method of delivery, or to complications of pregnancy. The infants were predominately males. The three



female infants exhibited a complete absence of uterus and vagina. The lungs of all infants were hypoplastic and the faces of all infants showed a characteristic expression. Prior to post-mortem examination only eight infants were believed to have died because of malformations.

The number of infants observed in this group of necropsies indicates that complete renal agenesis is not as rare as the small number of cases previously reported would indicate.

#### REFERENCES

1. Rosenbaum, R.: *Frankfurt. Ztschr. f. Path.* 41: 136, 1931.
2. Madison, H.: *Centralbl. f. allg. Path. u. path. Anat.* 60: 1, 1934.
3. Amolsch, A. L.: *J. Urol.* 38: 360, 1937.
4. Soloway, H. M.: *Ann. Surg.* 109: 267, 1939.
5. Hinman, F.: *Surg., Gynec. & Obst.* 71: 101, 1940.
6. Grimm, K. B.: *J. Urol.* 44: 397, 1940.
7. Nation, E. F.: *Surg., Gynec. & Obst.* 79: 175, 1944.
8. Stokes, G. D.: *Arch. Path.* 38: 220, 1944.
9. Potter, E. L.: *Am. J. Obst. & Gynec.* 51: 885, 1946.
10. Gruenwald, P.: *Anat. Rec.* 81: 1, 1941.

# LABORATORY AND CLINICAL CRITERIA OF RHEUMATIC CARDITIS IN CHILDREN

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IT HAS been suggested recently that in any public health program for rheumatic fever, an adherence to strict diagnostic criteria is of primary importance, but that "despite increase in knowledge of rheumatic fever, no specific diagnostic tests have been forthcoming."<sup>1</sup>

Obviously, in any workable program for the care and management of a disease of unknown etiology, a specific, clear-cut method for making a diagnosis is to be ardently desired. It is equally true, however, that when a definite diagnosis has been established, medical care and management will be guided by a clear recognition of all the evasive clinical and subclinical manifestations of the activity of the disease. The burdensome problems confronting physicians and public health officials are concerned with the meaning of rheumatic activity and its duration. When can one be certain that the disease has terminated? What are the diagnostic criteria for the cessation of the active rheumatic process?

It has been the common experience of students in this field that many patients, without obvious clinical or laboratory evidence of rheumatic activity, continue to show progressive cardiac damage. These patients have been suspected of having mild, clinically undetectable, active rheumatic disease. "Sub-acute carditis, which is insidious and subclinical, occurs more frequently than the acute phase of the disease."<sup>2</sup>

It is also widely held that the recurrence risk in rheumatic disease is significantly higher, the shorter the lapse of time from the cessation of the active rheumatic episode.<sup>3</sup> In addition, it is well known that patients having had active rheumatic carditis, have a greater recurrence risk than those without a history of carditis. These observations would seem to point to the necessity for a clear definition of rheumatic recurrence, with special reference to the reactivation defined as carditis. Does a patient have an early recurrence of rheumatic disease after an active episode or are the new clinical manifestations a continuation of the active process? The so-called "quiescent interval" might thus be considered as a form of mild rheumatic activity, presenting none of the classical and accepted criteria for rheumatic activity.

In recent years, many laboratory tests have been proposed to measure rheumatic activity. These have established in the mind of the general practitioner, a confident method of determining when the disease is no longer active. While it is widely known that none of these criteria singly, or in combination, can possibly act as an adequate screening method for rheumatic activity, a great reliance is placed upon them even by those who have seen, repeatedly, many exceptions to the rule. It is true that the student of rheumatic disease does not consider the many laboratory methods as specific tests

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From the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island.

for the diagnosis of the disease, but he is inclined to consider them as pertinent "in evaluating the presence of active rheumatic fever."<sup>1</sup>

It is the purpose of this paper to evaluate the laboratory aids in the diagnosis of active rheumatic carditis, and to describe some of the clinical criteria which have been found helpful in making a diagnosis of smoldering active rheumatic carditis in the absence of the usual positive laboratory evidence.

#### PATIENTS STUDIED

Two hundred boys and girls, 6 to 14 years of age, were observed at the St. Francis Sanatorium for Cardiac Children, from the beginning of an episode of rheumatic carditis to the end of the active process and for a minimum of six months following this period. All of these cases had a definite diagnosis established on the basis of both clinical and laboratory evidence. Children who showed clinical signs of heart failure were excluded from this study. Some of the children received only small doses of salicylates. This medication was discontinued as soon as the symptoms of arthralgia had subsided. The group received good nursing care, a balanced diet, and moderate amounts of synthetic vitamins. Any child who had an intercurrent infection or illness which might affect the clinical or laboratory course of the carditis, was excluded from this study. Thus the two hundred children were those who were admitted in the early part of an acute rheumatic episode, but who continued to present evidence of protracted carditis without obvious decompensation.

#### METHOD OF FOLLOW-UP

The work-up in each case consisted of a complete clinical and laboratory examination as well as cardiographic and immunologic studies. Repeated and frequent studies were made. It was soon discovered that many children who presented normal laboratory tests continued to show clinical evidence of carditis. Thus, no child was considered as being eligible for a return to normal activities until both laboratory and clinical evidence of active rheumatic carditis had subsided. When all of the children were considered as being quiescent, an analysis showed that in many cases none of the current laboratory tests used singly, or in combination, were helpful in arriving at a decision as to whether activity was present. Frequent, careful, clinical examinations of the patient thus became an essential part of the follow-up routine.

##### *I. Clinical and Laboratory Measurements.—*

A. *Leucocytosis*: The value of the leucocyte count as an index of rheumatic infection in children has been discussed for more than two decades.<sup>4</sup> Some observers found it helpful in the classification of the degree of rheumatic activity.<sup>5, 6</sup>

One in every ten of our cases showed no elevation of the white blood count at any time during the entire course of active rheumatic carditis. Nine of every ten showed a leucocytosis during the first two weeks after the onset of the illness, and seven of every ten continued to show such an elevation at the end of the fourth week. No leucocytosis was observed in any of our cases after the seventh week from the beginning of the active episode. All our

TABLE I. LABORATORY TESTS AND RHEUMATIC ACTIVITY

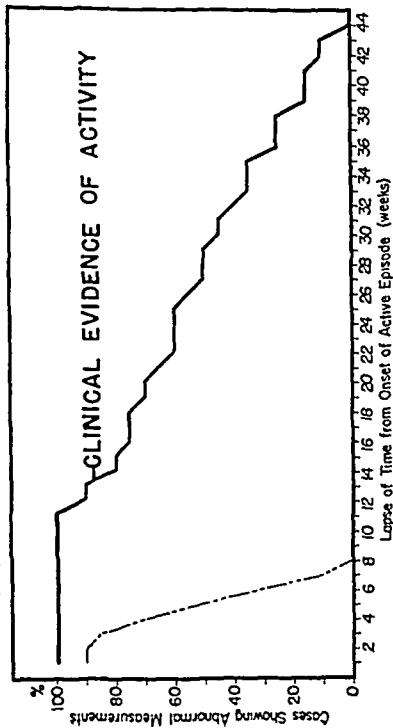
Percentage of cases showing abnormal laboratory measurements in relation to lapse of time from the onset of the active episode

LAPSE OF TIME FROM ONSET OF "ACTIVITY" (WK.)	WHITE BLOOD COUNT A	TEMPERATURE B	P-R INTERVAL C	PULSE RATE D	SED. RATE E	WEIGHT GAIN F	HEMOGLOBIN G	VITAL CAPACITY H	CLINICAL EVIDENCE OF "ACTIVITY"
1	90.0	100.0	82.5	100.0	100.0	100.0	100.0	90.0	100.0
2	90.0	90.0	82.5	100.0	100.0	100.0	100.0	100.0	100.0
3	85.0	60.0	82.5	100.0	100.0	100.0	100.0	100.0	100.0
4	70.0	25.0	80.0	100.0	100.0	90.0	100.0	100.0	100.0
5	50.0	20.0	80.0	100.0	100.0	90.0	100.0	100.0	100.0
6	30.0	20.0	80.0	100.0	100.0	90.0	100.0	100.0	100.0
7	10.0	20.0	80.0	100.0	90.0	90.0	100.0	100.0	100.0
8	0.0	20.0	80.0	100.0	85.0	90.0	100.0	100.0	100.0
9		20.0	80.0	92.5	85.0	85.0	100.0	100.0	100.0
10		20.0	80.0	90.0	85.0	85.0	100.0	100.0	100.0
11		10.0	80.0	90.0	85.0	85.0	100.0	100.0	100.0
12		10.0	80.0	80.0	75.0	85.0	85.0	100.0	90.0
13		0.0	75.0	75.0	75.0	85.0	85.0	100.0	90.0
14			75.0	50.0	75.0	85.0	85.0	100.0	80.0
15			50.0	30.0	75.0	85.0	85.0	100.0	80.0
16			45.0	30.0	75.0	85.0	80.0	75.0	75.0
17			30.0	30.0	75.0	60.0	80.0	75.0	75.0
18			20.0	30.0	75.0	60.0	80.0	75.0	75.0
19			15.0	30.0	75.0	50.0	80.0	75.0	70.0
20			5.0	30.0	75.0	50.0	80.0	70.0	70.0
21			5.0	20.0	70.0	50.0	70.0	70.0	65.0
22			1.0	20.0	60.0	50.0	65.0	70.0	60.0
23				20.0	55.0	50.0	60.0	70.0	60.0
24				20.0	50.0	40.0	50.0	60.0	60.0
25				20.0	40.0	40.0	30.0	60.0	60.0
26				10.0	30.0	40.0	30.0	60.0	55.0
27				10.0	30.0	40.0	30.0	60.0	50.0
28				8.0	20.0	20.0	20.0	60.0	50.0
29					20.0	20.0	20.0	60.0	50.0
30					20.0	20.0	20.0	60.0	45.0
31					5.0	10.0	15.0	60.0	45.0
32					0.0	0.0	0.0	50.0	40.0
33								35.0	35.0
34								20.0	35.0
35								10.0	35.0
36								0.0	25.0
37									25.0
38									25.0
39									15.0
40									15.0
41									15.0
42									10.0
43									10.0
44									0.0

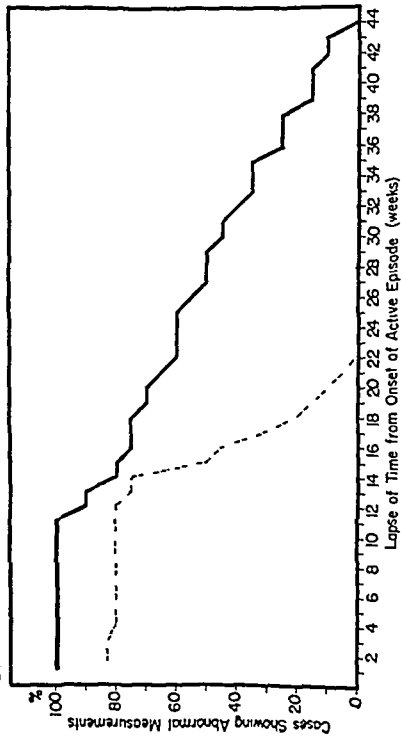
# NORMAL VALUES

Temperature: (Rectal) 97.5 to 99.5° F. (36.5 to 37.5° C.)  
White blood count: 7,000 to 8,500.  
Pulse rate: (Sleeping) 65 to 85 per min.  
P-R interval: (See Text, A-V Conduction).  
Erythrocyte sedimentation rate: 2 to 12 mm. per hour.  
Weight gain: Monthly gain according to age. (See reference.)  
Hemoglobin: 12.5 to 15.0 Gm.  
Vital capacity: (See reference.)

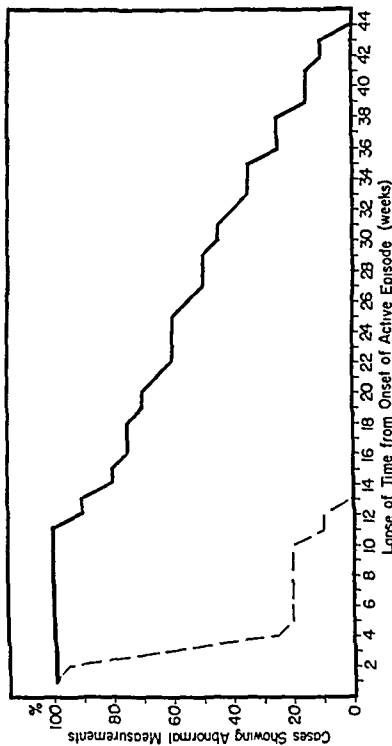
# A. LEUKOCYTOSIS



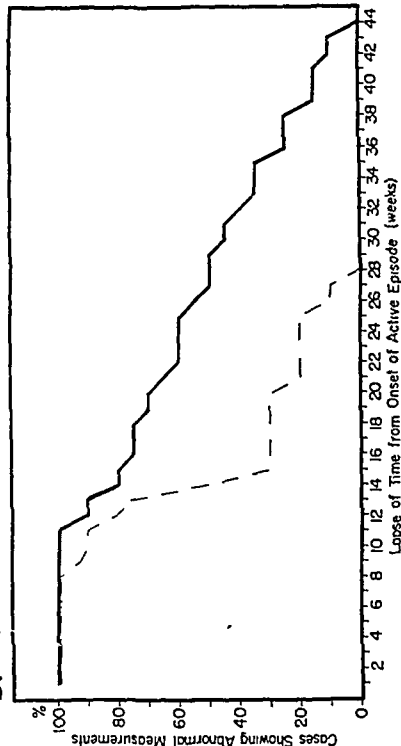
# C. A-V CONDUCTION



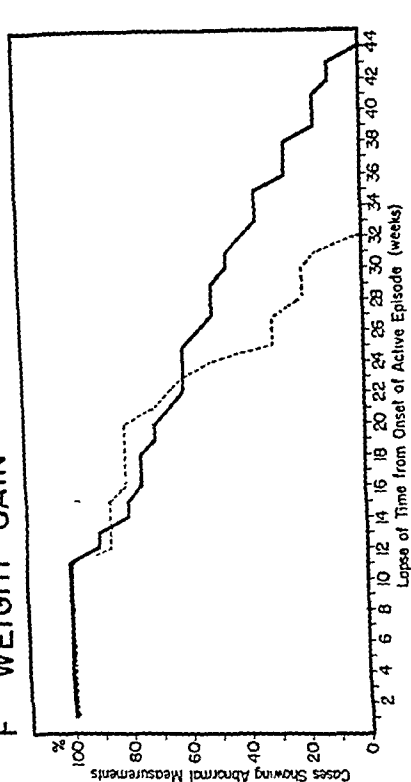
# B. FEVER



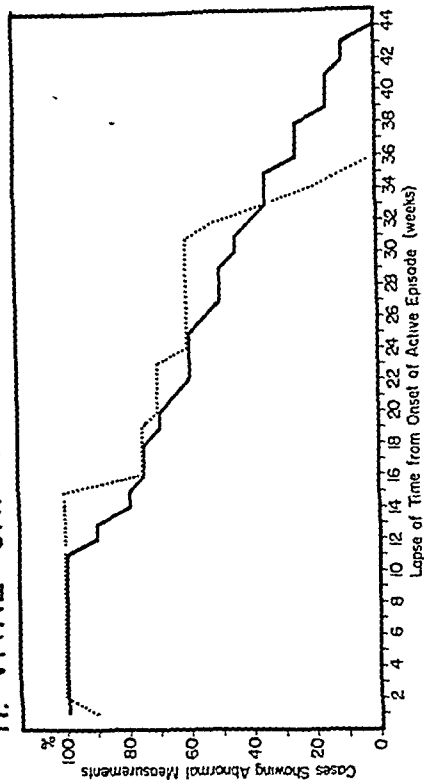
# D. PULSE RATE



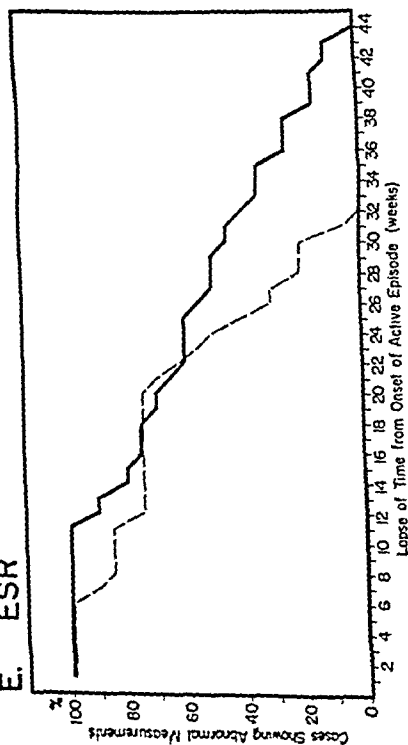
# F. WEIGHT GAIN



# H. VITAL CAPACITY



# E. ESR



# G. HEMOGLOBIN

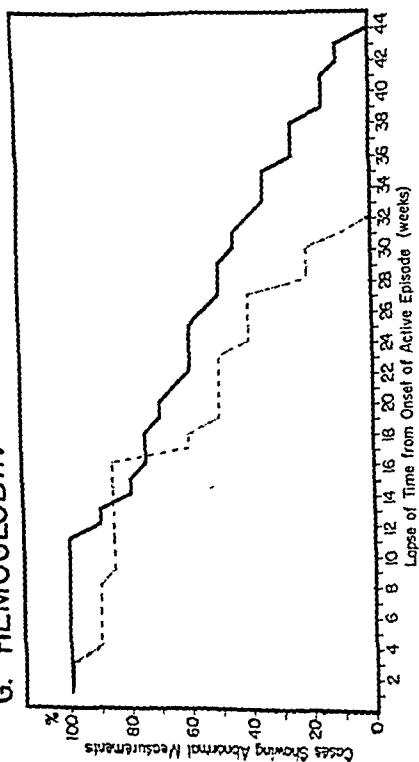


Fig. 1.—Percentage of cases showing abnormal laboratory measurements in relation to lapse of time from the onset of the active episode.

cases with a leucocytosis at the onset showed a definite decline in the total white blood count with the lapse of time from the onset. It is significant that, while all cases having a leucocytosis had obvious manifestations of clinical rheumatic activity, nine of every ten cases continued to show clinical evidence of active rheumatic disease after the total white blood count had returned to normal. (Table I, column A.) (Fig. 1, A.)

B. *Fever*: Both in private and hospital practice, a low-grade fever in a rheumatic patient is looked upon as a highly probable manifestation of rheumatic activity. A flat temperature curve is the commonest measurement upon which physicians rely in the assessment of the cessation of active rheumatic disease. Experience with rheumatic children shows that "fever alone is a common erroneous basis for a diagnosis of rheumatic fever."<sup>1</sup>

Fever as a significant manifestation of cessation of rheumatic carditis is not borne out by our observations. All of the cases showed a mild febrile course for a minimum of one week from the onset of activity. The greatest majority of patients, however, remained afebrile after the twelfth week from the onset of the acute process, and the average febrile period for the entire group was six weeks. Only one fifth (20 per cent) of the patients had a low-grade fever after the fifth week, and the longest febrile period was twelve weeks. It is of interest that those patients who showed a temperature level of more than 102° F. (38.9° C.) showed obvious signs of acute exudation, such as pericarditis, pleuritis, or definite joint manifestations, while those who had a fluctuating temperature at a level of less than 101° F. (38.4° C.) showed no such signs. While it is true that all the patients during the febrile period, showed obvious signs of active rheumatic disease, the greatest majority (90 per cent) continued to demonstrate rheumatic activity after the temperature was completely normal. (Table I, column B.) (Fig. 1, B.)

C. *Auriculoventricular Conduction*:<sup>6</sup> Disturbance in auriculoventricular conduction time has been considered as reliable evidence of the presence of active rheumatic disease in the auricular muscle. It has been suggested that this finding may be seen in the greatest majority of active rheumatic cases if frequent tracings are taken.<sup>7</sup>

The finding of a prolonged auriculoventricular conduction time in a rheumatic patient has come to be regarded as evidence of rheumatic carditis even in the absence of other laboratory or clinical evidence of rheumatic disease, and many a patient has been thus stigmatized, as long as his P-R interval has remained prolonged. On the other hand, a return of the P-R interval to normal is looked upon with confidence as a sign of cessation of rheumatic activity.

It is well known that a prolonged auriculoventricular conduction time may be of supracardiac origin.<sup>8</sup> In addition, long follow-up studies of patients with rheumatic disease show that some develop a prolonged A-V conduction as a permanent feature on their electrocardiographic tracing. In our experi-

*UPPER LIMIT OF NORMAL P-R INTERVAL BY AGE AND CARDIAC RATE					
AGE	70	71 TO 90	91 TO 110	111 TO 130	131 AND ABOVE
6 to 13	0.18	0.17	0.16	0.15	0.14
14 to 17	0.19	0.18	0.17	0.16	0.15

ence, a prolonged P-R interval in a rheumatic patient, without other laboratory or clinical signs of rheumatic disease, cannot safely be regarded as a manifestation of active rheumatic disease and the return of the conduction time to normal does not always mean cessation of activity.

Thirty-five (17½ per cent) of the children did not show any prolongation of the A-V conduction time at any time during the entire course of the active rheumatic process. It is probable that some of these might have shown a prolongation of conduction time, had electrocardiograms been taken at more frequent intervals. Ninety-nine per cent of the children who had a prolonged auriculoventricular conduction time at the onset of the carditis showed a normal conduction time later. However, 75 per cent of the cases showed clinical evidence of active rheumatic disease when the auriculoventricular conduction time had returned to normal. It is of some significance that two cases gave the impression of cessation of the active rheumatic disease, although the auriculoventricular conduction time was still prolonged. Both of these cases showed the same conduction time two years after the cessation of activity. (Table I, column C.) (Fig. 1, C.)

*D. Pulse Rate:*\* The fourth clinical manifestation of a return to normal following rheumatic activity was found to be the pulse rate. The elevation of the pulse rate was out of proportion to the elevation of the temperature, both in regard to the degree of elevation and to the period during which the pulse rate was found to be rapid. Thus, the children who had temperatures of 101 to 102° F. (38.4 to 38.9° C.) had an average pulse rate of 140. Similarly, other children whose temperatures had become normal, continued to have a pulse rate of 120 to 130.

The first three weeks after the onset of illness, the pulse rate was found to be higher than at any time thereafter. None of the two hundred cases showed a pulse rate of less than 100 before the end of the ninth week from the onset of the acute episode, and none had an elevated pulse rate twenty-seven weeks after the onset. The most marked decline in pulse rate was observed at the beginning of the tenth week following the onset.

It is noteworthy that four of ten children whose pulse rates remained normal, continued to show some evidence of active rheumatic disease. On the other hand, a few cases that were apparently quiescent, showed an occasional sinus tachycardia. (Table I, column D.) (Fig. 1, D.)

*E. Sedimentation Rate:* It is generally appreciated that an increase in the erythrocyte sedimentation rate is found in most toxic and infectious diseases. In rheumatic disease, an increase in the erythrocyte sedimentation rate has been considered as the most useful finding in evaluating the presence of rheumatic activity,<sup>1</sup> and some observers are inclined to look upon it as of specific diagnostic, as well as prognostic, significance in rheumatic fever.<sup>10-16</sup>

In our group of cases, the sedimentation rate was not as reliable a guide of rheumatic activity as is commonly reported. Many patients had definite

\*Most of these pulse rates have been taken during sleep.<sup>9</sup> It is presumed, therefore, that much of the emotional factor is excluded.



active rheumatic disease, with a normal sedimentation rate.\* All children showed marked elevation during the first eight weeks from the onset of the illness, the elevation being most marked during the first four weeks. At the end of eight weeks 15 per cent had normal sedimentation rates but many of these continued to show evidence of active rheumatic disease. After the twentieth week, an increasing number of children showed a normal sedimentation rate, and at the end of thirty-two weeks, the sedimentation rate became normal in all the cases, although 40 per cent of the group still showed some clinical evidence of mild rheumatic activity.

Of equal significance is the fact that at the end of the sixteenth week, a number of the children who failed to show clinical evidence of rheumatic activity, had a slightly elevated sedimentation rate. (Table I, column *E*.) (Fig. 1, part *E*.)

*F. Weight Gain:* Consistent gain in weight has been considered as indicative of the onset of the quiescent phase of rheumatic disease.<sup>2</sup> Our findings do not seem to substantiate this observation.

More than one-half of the children in our series were either normal or above normal weight at the beginning of the rheumatic episode. All children showed some loss in weight during the first eight or nine weeks of the active episode. Eighty-five per cent began to gain weight after the ninth week. Four months after the beginning of the illness, all children in this group were gaining weight consistently, but the average percentage of gain was less than would be expected for age, sex, and duration of the period of observation.

At the end of seven and one-half months from the onset, all children had reached a normal weight gain level,<sup>17</sup> although at this time, 40 per cent of them still showed mild rheumatic activity. During these seven and one-half months, a few children with apparently quiescent cases, failed to gain weight from month to month. This was found true mainly in the group of children below 8 years of age; the older age groups added weight in large amounts as soon as quiescence began. (Table I, column *F*.) (Fig. 1, *F*.)

*G. Hemoglobin:* Secondary anemia is usually present during rheumatic activity, the degree of anemia being related to the severity and the duration of the manifestations of the disease. It is considered a characteristic finding during active rheumatic carditis.<sup>18-21</sup>

All our cases showed a moderately severe anemia at the onset of the acute episode. During the first week, the hemoglobin ranged between 7 and 9 Gm. for the entire group. From the end of the first to the end of the fourth week, there was a further depression in the hemoglobin level so that at this time, the range was only 7 to 8 Gm. At the end of the fourth week, two of the children showed a hemoglobin of 5 Gm. It was only twelve weeks after the onset of the illness that thirty (15 per cent) of the children, showed a hemoglobin of 12.5 Gm. or more, and twenty-four weeks after the onset, one-half of them had a normal hemoglobin level. At the end of twenty-eight weeks, one of every five children still showed a low hemoglobin level, and it was only thirty-two weeks after the onset that the hemoglobin of all the children had returned to 12.5 Gm. or more.

\*No evidence of heart failure was observed in this group of children.

It may be said, therefore, that in our group of cases, none showed a normal hemoglobin at the beginning of the illness; the lowest hemoglobin level was found in the period from the second to the fifth week of the illness; and all the children showed a normal hemoglobin eight months after the onset of the illness. In a great many instances, the hemoglobin did not return to normal until the activity had subsided. On the other hand, 40 per cent of the cases showed clinical evidence of rheumatic activity after the hemoglobin had returned to normal. (Table I, column G.) (Fig. 1, G.)

H. *Vital Capacity*:<sup>2</sup> It is generally agreed that a diminishing vital capacity is one of the earliest signs of left ventricular failure.<sup>22</sup> It has been suggested that a low vital capacity in a rheumatic patient, when all other factors which might influence the vital capacity are excluded, is to be considered as a good index of rheumatic activity in the heart muscle.<sup>23, 24</sup> The reduction of the vital capacity in a rheumatic patient is looked upon as a measure of left ventricular failure, even in the absence of the more obvious signs and symptoms of cardiac insufficiency.

The vital capacity in this group of children seems to be the single index most sensitive of the progress of active rheumatic disease. All children showed a vital capacity of 40 per cent or less below normal for age and body surface.<sup>†</sup>

For the first three months of the rheumatic activity, none of the children showed a rise in vital capacity. Some began to have a slight elevation three months after the onset of activity. The rise was small and the number of cases few. After the first three months, more cases showed a gradual rise in vital capacity, but none reached normal for age and body surface until sixteen weeks following the onset of rheumatic carditis. At this time, one of every four children had a normal vital capacity. The last case which returned to a normal vital capacity reading was eight and one-half months after the onset. On the other hand, even after this lapse of time from the onset, one-fourth of the children still showed mild clinical evidence of rheumatic activity. Thus, while the vital capacity was the last measurement to return to normal, yet it failed to be a specific diagnostic measurement, as many of the children continued to show clinical evidence of active rheumatic disease, while having a normal vital capacity.

A few children had a low vital capacity but failed to show clinical evidence of rheumatic active disease on repeated examination. (Table I, column H.) (Fig. 1, H.)

*Summary*: In summary, then, those laboratory measurements upon which considerable reliance is placed in evaluating the progress of active rheumatic disease, did not seem to be adequate for a diagnosis of activity in our group of cases. At the end of nine months from the onset of rheumatic activity, all children in the group showed normal laboratory data, and yet, a large percentage continued to demonstrate clinically, rheumatic carditis.

Some of the clinical measurements remained abnormal for a longer period after the onset than others. None were adequate in screening all cases of

\*Children below 8 years of age were excluded from this group since the vital capacity reading is unsatisfactory at this age level.

†Vital capacity measurements were evaluated according to the chart presented by Dr. May G. Willson.<sup>2</sup>

active rheumatic carditis. Finally, in some cases, an abnormal laboratory test is registered in an otherwise quiescent patient.

## II. *Clinical Observations and Criteria.*—

*Appearance of Patient:* Fatigability, without evidence of cardiac insufficiency, is the symptom which can be adjudged best from careful observation of the patient, rather than from a provocative inquiry into symptoms of fatigue. The child, who under normal circumstances is anxious to participate in all childhood activities during mild active rheumatic disease devises ways and means for substitution of less vigorous and in some instances completely circumscribed activities, provided he is given the chance to do so.

Emotional instability, which is a concomitant of active rheumatic carditis, capricious appetite, restless sleep, and disturbance in the habits of evacuation and urination, form part of the syndrome of mild rheumatic activity. Marked and frequent fluctuations of expressions of elation and depression are obvious manifestations during this phase of the disease.

From time to time, there appears in the literature, the observation on the part of the clinician that the rheumatic patient presents a typical appearance. The pallor of active rheumatic disease during the acute stage is well known. This is often far greater than one would expect from the level of the hemoglobin.

The discrepancy between the degree of pallor and the level of the hemoglobin continues during the entire active rheumatic process, even in the smoldering phase, when all other signs of activity seem to have come to an end. A close parallelism exists between the degrees of pallor and of fatigability. Afternoon and evening pallor is of greater intensity than that noted after a night's rest. Increase in physical exertion or emotional disturbance accentuates the pallor after the initial increase in coloring following exertion.

These three manifestations are a definite part of the general picture which is presented by the patient who is suffering from mild rheumatic activity. As long as the patient presents these manifestations, active rheumatic disease must be suspected.

*Auscultatory Evidence:* A marked tachycardia with a tumultuous rhythm has long been recognized in acute rheumatic disease as auscultatory evidence of carditis. A clearly defined gallop rhythm with a rapid or slow cardiac rate has also been considered as evidence of an acute carditis. And, in recent years, a rapid evolution of progressive cardiac damage, i.e., cardiac dilatation and hypertrophy, and increase in the extent of the valvulitis with rapidly advancing signs of cardiac insufficiency, has been looked upon as criteria of acute rheumatic carditis.

The absence of a tachycardia, gallop rhythm, and clear evidence of rapidly progressive cardiac damage in a rheumatic child, is thus considered as confident auscultatory evidence that carditis is at an end.

Frequent and careful observation of large groups of children from the onset to the end of an attack of acute carditis gave the impression that the criteria as described are inadequate in making a diagnosis of a mild smoldering carditis. One of every three cases of carditis failed to show this evidence.

Continuous and detailed follow-up studies of this group showed other auscultatory signs, not clearly defined but apparently significant of an active process in the heart muscle.

The cardiac rates in this group of children were rapid or slow, but always markedly labile. Stimuli, which in quiescent hearts did not disturb the cardiac rate, caused, in this group, marked fluctuations. Furthermore, this fluctuation was of long standing. Physical exertion and emotional disturbance produced a sinus tachycardia of the ticktack type, lasting several hours. Continued bed rest might slow the heart rate to the normal average, only to be markedly accelerated when bed rest was terminated. When, however, active carditis had subsided, this disturbance in cardiac rate was of distinctly lesser degree and of markedly shorter duration. In a quiescent carditis, the return to normal of the accelerated heart rate was measured in terms of minutes; in active carditis, it was measured in terms of hours and, not infrequently, in terms of days.

Cardiac sounds and murmurs in mild carditis were ever-changing. The volume and pitch of both first and second heart sounds varied from day to day and often from beat to beat. Murmurs changed in quality, direction, and extent of transmission. The evanescent character of cardiac murmurs in rheumatic hearts is well known. The frequency and multiplicity of changes observed in this group of children were noted only in the actively inflamed hearts. It would seem that the cardiodynamics responsible for cardiac sounds and murmurs are in a state of flux in active carditis, and stabilize when the disease becomes quiescent.

The cardiac rhythm in active carditis simulates that of an embryocardia, irrespective of the rate. The normal ratio of the duration of systole and diastole is definitely disturbed. The usual one-to-two rhythm is lost and approaches more nearly, a one-to-one rhythm. On auscultation, it would seem that the time interval between the first and second heart sounds is equivalent to the interval between the second and first sounds. It is well known that during exercises, the diastolic period is foreshortened to a greater degree than the systolic period, but the sinus tachycardia after exercises or during fever is distinct from the embryocardia type of rhythm noted in carditis. And this type of rhythm is not modified by cardiac rate, as long as carditis continues. Occasionally, a sinus bradycardia with a one-to-one rhythm is observed in active carditis.

As rheumatic activity subsides, the disturbance in rhythm gradually returns to normal. The restoration period to the normal ratio is slow and unstable. In complete physical and emotional rest, the patient, who is definitely approaching quiescence, shows short periods of normal cardiac rhythm. Diastole becomes relatively longer. These periods of normal rhythm are punctuated by intervals of the ticktack variety of rhythm. At this stage, physical exertion or emotional disturbance blots out the periods of normal rhythm and the tumultuous character of the cardiac action is accentuated.

The unstable character of the cardiac rate, the evanescent character of sounds and murmurs, and the disturbance in rhythm were noted in all of our

cases during the initial phase of the acute carditis. In one of every four cases, these auscultatory signs persisted after all laboratory evidence of rheumatic activity had subsided. It is of great significance from the therapeutic standpoint, to note that the group of children showing only auscultatory evidence of carditis, did poorly when permitted to resume normal childhood activities. Some showed symptoms of cardiac insufficiency and a few presented unequivocal evidence of cardiac enlargement after a short period of observation. Many children in this group began to show obvious signs of reactivation. The auscultatory signs of carditis increased and corroborative laboratory evidence became manifest. When, however, all auscultatory signs of carditis had definitely subsided, a return to normal physical activity presented no untoward effects and signs of rheumatic reactivation were not observed.

#### COMMENT

There is solid evidence that bed rest is the important form of treatment for rheumatic carditis. We are impressed with this concept, notwithstanding the modern tendency to shorten bed rest in cardiac disease. This observation is based upon a large experience with rheumatic children. If management and care of rheumatic carditis is predicated upon this conviction, the importance of diagnostic criteria for rheumatic carditis is obvious. Of even greater importance then, would be the introduction of clear-cut criteria for the cessation of active rheumatic disease. For, once one is certain that the active inflammatory process in the heart muscle has subsided, management can safely be changed from bed rest to normal activities without fear of encouraging further cardiac damage.

In the last few years, much reliance has been placed upon certain laboratory measurements used as criteria for evaluation of the progress of active rheumatic disease. These, we believe, have been placed in improper perspective, relative to their significance as diagnostic criteria. None of the currently used clinical measurements, singly or in combination, can be used as specific diagnostic criteria for active rheumatic carditis.

While abnormal clinical measurements are recorded in all cases of acute carditis at the onset, it is obvious from this group of cases that all of the tests became normal in 25 per cent of the children before the cessation of carditis. It is also apparent that a few cases show no clinical evidence of active carditis while some of the laboratory measurements are still abnormal. These observations would seem to point to the concept that our current laboratory measurements may not be a specific expression of the acute process, but rather a manifestation of specific host-reaction to a disease process. Some patients show a high degree of adaptation to the disease process. In these, the abnormal laboratory measurements return to a normal level readily, although the disease process continues. Other patients show a poor adaptation in this respect. In these, the laboratory measurements continue to be abnormal for a longer period. A few individuals continue to manifest laboratory abnormalities after the disease process has subsided.

Experience with the cases presented in this paper once again brings to the foreground the fact that final decision, as regards the presence or absence of active rheumatic disease, rests upon clinical judgment. This, as in all other medical problems, is a product of continued careful observation and examination of large numbers of children with rheumatic disease over the entire period of rheumatic activity, and for years following the active episode. We are impressed with the observation that clinical assessment of the patient as a whole and careful evaluation of auscultatory findings in an actively inflamed rheumatic heart, are more nearly accurate screening methods for mild rheumatic carditis than those laboratory tests currently adhered to.

## SUMMARY

1. Two hundred children with rheumatic carditis were studied under controlled conditions.

2. The observation was made that laboratory measurements, such as temperature, white blood count, pulse rate, auriculoventricular conduction, sedimentation rate, weight, hemoglobin, and vital capacity, are inadequate in finally determining when active carditis has ceased.

3. Clinical judgment and careful observation of the patient and his heart add 25 per cent more cases with a diagnosis of active rheumatic carditis, when all laboratory criteria have failed.

## REFERENCES

1. Jones, T. D.: J. A. M. A. 126: 481, 1944.
2. Wilson, M. G.: Rheumatic Fever. The Commonwealth Fund, New York, 1940, p. 157.
3. Wilson, M. G., and Lubschez, R.: J. A. M. A. 126: 477, 1944.
4. Wilson, M. G., and Kopel, M.: Am. J. Dis. Child. 32: 46, 1926.
5. Swift, H. F., Miller, C. P., Jr., and Boots, R. H.: J. Clin. Investigation 1: 197, 1924.
6. Juster, I. R.: Am. Heart J. 17: 669, 1939.
7. Cohn, A. E., and Swift, H. F.: J. Exper. Med. 39: 1, 1924.
8. Keith, J. D.: Quart. J. Med. 7: 29, 1938.
9. Struthers, R. R., and Bacal, H. L.: Canad. M. A. J. 29: 470, 1933.
10. Kahlmeter, G.: Klin. Wchnschr. 5: 889, 1926.
11. Sharpless, F. C.: Atlantic M. J. 31: 10, 1927.
12. Ernstene, A. C.: Am. J. M. Sc. 180: 12, 1930.
13. Hill, N. G.: Brit. J. Child. Dis. 29: 181, 1932.
14. Elghammer, H. W.: Arch. Pediat. 51: 281, 1934.
15. Perry, C. B.: Arch. Dis. Childhood 9: 285, 1934.
16. Payne, W. W., and Schlesinger, B.: Arch. Dis. Childhood 10: 403, 1935.
17. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, ed. 8, New York, 1922, D. Appleton-Century Company, Inc., p. 22.
18. Hubbard, J. P., and McKee, M. H.: J. PEDIAT. 14: 66, 1939.
19. Gezelius, G.: Svenska läk.-tidning. 55: 873, 1938.
20. Gezelius, G.: Acta paediat. 23: 361, 1939.
21. Gwyn, N. B.: Canad. M. A. J. 37: 117, 1937.
22. Peabody, F. W.: Am. J. M. Sc. 155: 100, 1918.
23. Wilson, M. G.: M. Clin. North America 8: 199, 1924.
24. Wilson, M. G., and Edwards, D. J.: Am. J. Dis. Child. 22: 443, 1921.

## IMMUNIZATION AGAINST WHOOPING COUGH

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RECENT public health studies<sup>1, 2</sup> on the efficacy of prophylaxis against whooping cough attest to its value, so that by now practically all pediatricians include this immunization, together with diphtheria inoculations and smallpox vaccination, as routine in the care of well children. However, the results, when critically evaluated, are not so good as with prophylaxis against diphtheria. The communicability rate after pertussis immunization remains at 31 to 39 per cent of that for the controls. A re-examination of certain details of immunization has therefore seemed wise. Factors studied were: (1) the age at which immunization was begun; (2) the type of vaccine used; (3) the time interval between injections; (4) the concentration of the vaccine; and (5) the total dosage administered.

(1) *Desirable Age*.—The high mortality rate of whooping cough in the first year of life has led to a number of efforts to secure immunity in very young infants. The inoculation of pregnant mothers with *Hemophilus pertussis* vaccine has been claimed<sup>3, 4</sup> to produce passive immunity in the newborn, but the short life of passive immunity and the lack of clinical evidence of protection seem to have stopped this method. Sauer's<sup>5</sup> experience was discouraging; 8.19 per cent of the infants inoculated under 3 months of age contracted pertussis, as compared with 1.44 to 2.8 per cent for children vaccinated after 7 months of age. Recently, Sako and associates,<sup>6</sup> injecting 3,793 infants under 3 months of age with a total of 40 billion bacteria in the form of alum-precipitated pertussis vaccine, found that 75 per cent of these young infants showed antibody response, as measured by the rapid slide agglutination method.<sup>7</sup>

On the other hand, Miller and associates,<sup>11</sup> using 40 billion *H. pertussis* in aluminum hydroxide as the total dose, "failed to lift the desired 90 per cent of the sera over the 1:320 agglutinin titer level." Their method, being quantitative, is probably more nearly accurate than that of Sako and associates.<sup>6</sup>

It must be re-emphasized that agglutinins, complement fixing antibodies, and opsonins are not protective antibodies, and may or may not measure immunity. Only when a sufficient interval of time has passed to judge clinical immunity (perhaps five years) will it be possible to decide whether true immunity has resulted in these young infants.

To test this question, 20 infants from 3 to 6 months of age received 120 billion *H. pertussis* vaccine in three doses at four-week intervals. Three months later, rapid agglutination tests<sup>7</sup> were performed (Table I). The blood of three infants (15 per cent) was 4 plus; the blood of five infants (25 per cent) was 3 plus; and the others (60 per cent) were negative. Thus, only 40 per cent of the infants immunized between 3 and 6 months of age were positive, whereas when inoculations are postponed until after 6 months of age, from 90 to 95 per cent are positive.

TABLE I.—RAPID AGGLUTINATION TESTS ON INFANTS FROM 3 TO 6 MONTHS OLD RECEIVING 120 BILLION *H. PERTUSSIS* VACCINE

TOTAL INFANTS	NEGATIVE	3 PLUS	4 PLUS
20	12	5	3
Percentages	60.0	25.0	15.0

(2) *Type of Vaccine.*—The type of vaccine to be used in immunization aroused much discussion in previous years. U.B.A., Pertussis Antigen and Topagen, each had their proponents until Dow<sup>5</sup> showed that all these vaccine fractions lost a considerable portion of their antigenicity. Alum-precipitated vaccines, especially mixtures of *H. pertussis* and diphtheria toxoid, have had a vogue recently, due especially to the insistence of Sauer and associates,<sup>9</sup> that severe reactions could be minimized with "the needle directed distally." Sako and associates,<sup>6</sup> using the small dosages of 8, 12, and 20 billion of the alum-precipitated vaccine in 3,793 infants, observed reactions in 3.3 per cent of the first inoculation, 9 per cent of the second, and 13.6 per cent of the third, with an average of 0.6 per cent abscess formation. They disagree with Sauer and associates stating that the greatest factor in abscess formation was intracutaneous introduction of the alum-precipitated vaccine. Anyone who has seen a number of alum abscesses<sup>10</sup> produced, no matter how the injection is given, will not be so certain. The low pH of alum vaccines, seems to summate the necrotizing power of *H. pertussis*, so that 25 per cent or so produce severe reactions, and 5 per cent produce abscesses.

Semoff,<sup>12</sup> in a comparison of commercial combined or multiple vaccines with fluid toxin, found reactions with alum solutions to be generally more severe and to cause nodules and abscesses, whereas plain fluid toxins gave the best results of all.

This objection to mixed vaccines does not apply to the mixtures of whooping cough vaccine with fluid diphtheria toxoid nor to the mixtures made with aluminum hydroxide (Cutter method). These have been distinctly useful in a technique different from any cited. If the first injection of whooping cough vaccine (40 billion) produced marked pain or fever, the remainder of the 80 billion *H. pertussis* was given in 5 doses of 16 billion each, mixed with 0.5 c.c. fluid diphtheria toxoid. This resulted in a distinct diminution of reactions. Another type of mixed vaccines, the so-called triple immunization, or 3 in 1, against whooping cough, diphtheria, and tetanus in a mixture with aluminum hydroxide<sup>11</sup> resulted, in my experience, in a slightly larger percentage of reactions when used for routine immunization, but it proved very useful for the booster doses given every second year or so. In such cases, the minimal quantities needed for the booster dose resulted in only mild reactions. Thus, if due weight be given to reactions, only the plain *H. pertussis* vaccines of the Sauer (human), Kendrick (sheep), Lilly (bovine), and Cutter (human) types should be given. The possibility of sensitization to vaccines harvested on other than human blood seems to have been nihilized by theoretical demonstration of the improbability of such a phenomenon<sup>13</sup> as well as by the practical experience of many thousands of inoculations. Reactions will occur with any of these vaccines.



but usually they are mild. Occasionally, an infant will respond to the first inoculation with much discomfort and high fever; in these cases, giving the smallest possible quantities in divided doses usually serves to minimize the reactions.

(3) *The Total Dosage.*—The results obtained by Miller and associates,<sup>11</sup> with quantitative agglutination tests, show that even where aluminum hydroxide mixtures are used, a total dosage of 40 billion is frequently insufficient. This must be reiterated, because, unfortunately, many of the commercial mixtures on the market prescribe total dosages of *H. pertussis* clearly insufficient for adequate immunization. The total dosage to be given was originally set by Sauer at 80 billion, but serologic tests<sup>14</sup> showed that a fair percentage of children needed 110 to 140 billion for complete immunization and clinical results of exposures<sup>15</sup> seemed to show that 80 billion were frequently insufficient, while 130 billion usually resulted in complete protection. In a three-year period, the communicability rate of 200 infants the author inoculated with 120 billion was only 9.6 per cent (Table II) as compared with an average of 31 to 39 per cent for those given 80 billion in a previous three-year period.<sup>1</sup>

TABLE II.—COMMUNICABILITY RATE OF 200 INFANTS FROM 6 TO 9 MONTHS OLD RECEIVING 120 BILLION *H. PERTUSSIS* VACCINE, IN THREE-YEAR STUDY

TOTAL DOSAGE	INTIMATE EXPOSURES	ACQUIRED DISEASE	COMMUNICABILITY RATE
120 billion	52	5	9.6%
80 billion	56	19	33.9%

(4) *The Time Interval Between Inoculations.*—The time interval between inoculations was originally set by Sauer as a week. Clinical results and complement fixation tests<sup>16</sup> suggested that protection would be definitely greater if four-week intervals were employed. This is in line with current immunologic practice in diphtheria and tetanus inoculations.

(5) *The Concentration.*—The concentration or dilution of vaccine employed has similarly experienced many variations in popular favor. The original concentration of 10 billion *H. pertussis* to the cubic centimeter was raised to 20 billion, but the claim that this produced too many reactions resulted in lowering the concentration to 15 billion per cubic centimeter. If 120 billion are to be given, this would necessitate 8 c.c., presumably given as 2 c.c., 2 c.c., and finally 2 c.c. in each arm. No critical analysis of this factor of concentration has appeared in the literature. For this reason, a vaccine with a concentration of 40 billion *H. pertussis* to the cubic centimeter (Cutter) was employed in inoculation of one group of 100 children with 1 c.c. doses at four-week intervals, a total of 120 billion. A second group of 50 children was given 2 to 4 c.c. injections of the 15 billion concentration, and the last group of 50 children was given three 2 c.c. injections of a 20 billion concentration. (Table III.) Each mother was asked to keep a record of evident pain experienced by the infant, to measure the area of inflammatory reaction on the arm, and to record the temperature three times in the twenty-four hours after the inoculation. With a 40 billion concentration of vaccine, 24 per cent experienced pain, 10 per cent showed local induration,

and 21 per cent showed fever above 100° F. With a 15 billion concentration, 30 per cent experienced pain, 12 per cent showed local swelling, and 25 per cent had fever. With a concentration of 20 billion, 25 per cent had pain, 10 per cent showed local swelling, and 25 per cent had fever. These results seem to show no difference in reaction, no matter what the concentration of vaccine employed, at least in a range from 15 billion to 40 billion per cubic centimeter.

TABLE III.—REACTIONS IN THREE GROUPS OF CHILDREN GIVEN VARYING CONCENTRATIONS OF *H. PERTUSSIS* VACCINE, WITH AN AVERAGE OF THREE INOCULATIONS

	NUMBER	PERCENTAGE PAIN	PERCENTAGE LOCAL INDURATION	PERCENTAGE FEBRILE REACTIONS
Group I.—40 billion concentration; 3 doses of 1 c.c. at four-week intervals	100	24	10	21
Group II.—15 billion concentration; 2 c.c.; then 2 c.c.; and finally 4 c.c. at four-week intervals	50	30	12	25
Group III.—20 billion concentration; 3 doses of 2 c.c. at four-week intervals	50	25	10	25

The differences are statistically insignificant. The question is whether the extra volume introduced by lowering the concentration of vaccine (for a 15 billion concentration, 8 c.c. as compared with 3 c.c. of a 40 billion concentration). does not produce tissue damage which compensates for the concentration.

#### SUMMARY

An effort to lower the communicability rate of infants immunized with *H. pertussis* in the usual fashion has led to a critical evaluation of certain factors in this routine immunization.

First, the optimum age at which to start immunization for pertussis remains 6 to 9 months. Theoretical analogy with other immunizations and Sauer's discouraging results under 6 months, more than counterbalance the recent report of Sako and associates. In a small group, (20) infants from 3 to 6 months of age, this paper shows a failure of protection as judged by agglutination tests. Until clinical evidences of immunity are forthcoming, as judged by actual protection to exposure, infants should not be inoculated before 6 months of age.

Second, the type of vaccine to be used is reviewed. The use of alum-precipitated vaccines of *H. pertussis* is condemned on the ground of frequent severe reactions, and occasional abscess formation. Sako and associates, using a total dose of only 40 billion, found abscess formation in 0.6 per cent. If the dosage of 80 to 120 billion commonly accepted as necessary for clinical protection were employed, the abscess formation might reach as high as 10 per cent, in the author's experience. The use of combined vaccines, *H. pertussis* with diphtheria toxoid, or with diphtheria toxoid and tetanus toxoid is also condemned on the same ground if the vaccine is alum-precipitated.

Third, the total dosage to be given, originally set at 80 billion, is now recommended to be 120 billion, both on serologic and clinical results cited.

Two hundred infants from 6 to 9 months of age, given 120 billion, showed a communicability rate of only 9.6 per cent as compared with an average of 33.9 per cent for those given 80 billion.

Fourth, the time interval between inoculations, originally set at one week apart, is now recommended to be four weeks apart, both on serologic and clinical experience cited from the literature.

Fifth, the concentration of the vaccine to be employed, originally set at 10 billion to the cubic centimeter, is now recommended to be 20 or 40 billion to the cubic centimeter. A study of three groups of children inoculated with 15, 20, and 40 billion concentrations, with a total dosage of 120 billion, showed statistically insignificant variations in reactions, as judged by pain, local swelling, and fever.

#### REFERENCES

1. Lapin, J. H.: Whooping Cough, Springfield, Ill., 1943, Charles C Thomas, Publisher, p. 164.
2. Garvin, J. A.: Ohio State M. J. 36: 738, 1940.
3. Cohen, P., and Scadron, S. J.: J. A. M. A. 121: 656, 1943.
4. Kendrick, P., Thompson, M., and Eldering, G.: Am. J. Dis. Child. 70: 25, 1945.
5. Sauer, L. W.: Am. J. Path. 17: 719, 1941.
6. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S. J.: J. A. M. A. 127: 379, 1945.
7. Powell, H. M.: J. Indiana M. A. 37: 563, 1944.
8. Dow, R. P.: Canad. Pub. Health J. 31: 370, 1940.
9. Sauer, L. W., Tucker, W. H., and Markley, E.: J. A. M. A. 125: 949, 1944.
10. Lapin, J. H.: J. PEDIAT. 22: 439, 1943.
11. Miller, J. J., Jr., Humber, J. B., and Dowrie, J. O.: J. PEDIAT. 24: 281, 1944.
12. Semoff, M.: Rocky Mountain M. J. 41: 735, 1944.
13. Mishulow, L., Mowry, I., and Orange, R.: J. PEDIAT. 9: 492, 1936.
14. Daughtry-Denmark, L.: Am. J. Dis. Child. 52: 587, 1936.
15. Lewis, J. M., Barenberg, L. H., Greenspan, L., and Greenberg, B.: J. PEDIAT. 17: 585, 1940.
16. Lapin, J. H., Cohen, P., and Weichsel, M.: Arch. Pediat. 56: 590, 1939.

## CRANIOPHARYNGIOMAS IN CHILDREN

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THE CRANIOPHARYNGIOMAS constitute a small but important group of the intracranial neoplasms encountered in childhood. As reported in the literature they comprise about 13 per cent of such tumors. Since they may produce blindness, severe disorders of growth and metabolism, and obstruction to the ventricular system they are important to the pediatrician. To the neurosurgeon they are of extreme importance because they are benign lesions, and hence, theoretically, curable ones. However, because of their environmental relations, the difficulties they present were felt by Cushing<sup>1</sup> to "... offer the most baffling problem which confronts the neurosurgeon."

These tumors are described in the literature by a variety of names suprasellar cysts, craniobuccal cysts, Rathke's pouch tumors, adamantinomas, hypophysial duct tumors, interpeduncular cysts, suprasellar epitheliomas, craniopharyngeal duct tumors. Excellent studies of these neoplasms have been made by Duffy,<sup>2</sup> Critchley and Ironside,<sup>3</sup> McLean,<sup>4</sup> Beckmann and Kubie,<sup>5</sup> Frazier and Alpers,<sup>6</sup> and by Love, Shelden, and Kernohan.<sup>7</sup>

The relationship of the so-called craniopharyngiomas to the hypophysial duct was first suggested by Mott and Barrett<sup>8</sup> in 1899, and later established by Erdheim<sup>9</sup> in 1904. Erdheim pointed out that in the embryonic development of the hypophysis from a union of infundibular and buccal pouch components the epithelium comprising the original forward wall of Rathke's pouch comes eventually to form the anterosuperior covering of the anterior lobe of the hypophysis. (Fig. 1.) Squamous cell rests occupying this location have been observed repeatedly in autopsy studies in the absence of neoplasm. Proliferation of these squamous epithelial cells results in the epithelial masses with cyst formation that are known as suprasellar cysts, hypophysial duct tumors, adamantinomas, and craniopharyngiomas. Cushing coined the term "craniopharyngioma" because he felt it was accurately descriptive of the tumor's unique origin. Bremer<sup>10</sup> recently pointed out that from the embryologic point of view this widely accepted term is not accurate, since Rathke's pouch is a diverticulum of the buccal cavity and not of the embryonic pharynx (Fig. 2). The mucosa of the stomodeum is of ectodermal origin and not entodermal as is that of the pharynx. Thus, the hypophysial duct tumors owe their masses of squamous cells to the ectodermal lining of the buccal cavity or stomodeum. The term craniostomodeal cyst is a more nearly accurate designation of these tumors. It seems hardly worth while to suggest the substitution of a new name when craniopharyngioma is well established and clearly understood, even though actually inaccurate.

Sixteen children with craniopharyngiomas have been treated by the surgical services of The Children's Hospital and the Peter Bent Brigham Hos-

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pital during the thirteen-year period of 1932 to 1945 inclusive. This report, from experience with these 16 children, is concerned with the problems encountered and the clinical aspects of craniopharyngiomas in early life. Two case reports will be followed by a general discussion of the problem.

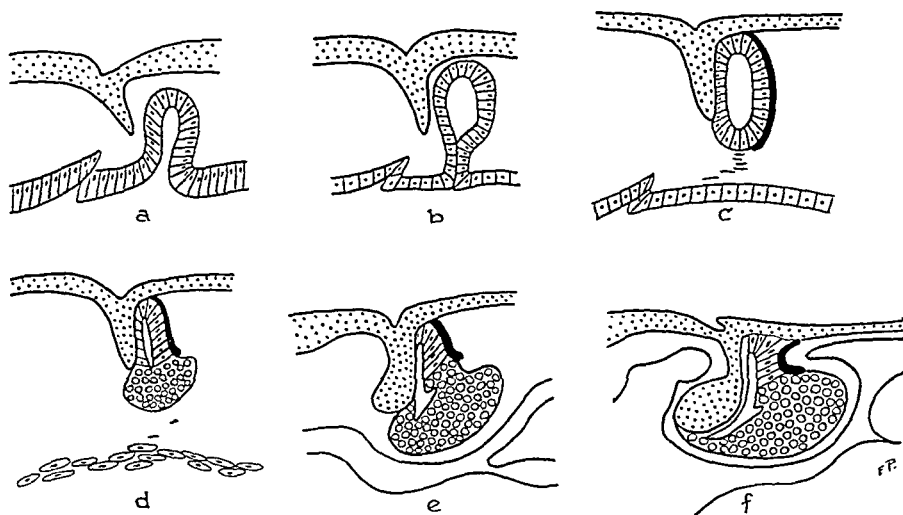


Fig. 1.—Stages in the embryonic development of the hypophysis. Note how the forward wall of Rathke's pouch (heavy black line) comes to form the anterosuperior covering of the hypophysis.

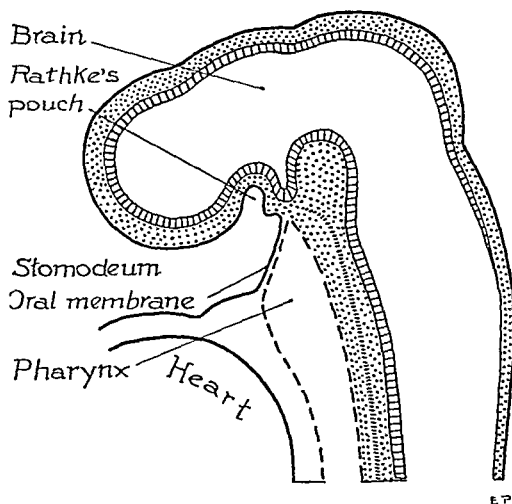


Fig. 2.—Diagram of 2.2 mm. embryo to illustrate the relationship of Rathke's pouch to the stomodeum.

#### CASE REPORTS

CASE 1.—(A rather typical case of craniopharyngioma in a female child.)

*First Admission:* N. T. (C. H. #254725). A 6-10/12-year-old girl was admitted to The Children's Hospital on Aug. 20, 1941, because of headaches and vomiting of six months' duration. Past history and family history were irrelevant. Growth and development were normal. The child had been well until six months before admission when she developed mild frontal headaches, occasionally associated with vomiting. She had no visual disturbance,

diabetes insipidus, anorexia, weight loss, ataxia, or paralysis. Headaches and vomiting spells became worse and medical attention was finally sought. Roentgenograms of the skull taken in another hospital revealed separated sutures and calcification above the sella turcica. The child was referred to The Children's Hospital with a diagnosis of craniopharyngioma.



Fig. 3.—Case 1 (N. T.) at time of initial hospitalization, Aug. 20, 1941.

Physical examination on admission revealed an alert, cooperative little girl in a good nutritional state (Fig. 3). Heart, lungs, and abdomen were normal. On neurological examination the positive findings included a positive Macewen's sign, bilateral papilledema of 2 diopters, and hyperactive but equal reflexes. Visual fields were normal. The remainder of the examination showed no abnormalities.

Routine laboratory studies of blood and urine were not remarkable. Blood Hinton test was negative, as was a tuberculin test. Roentgenograms of the skull showed an irregular area of calcification measuring about 1.3 by 0.9 cm. in size, extending upward from the sellar fossa (Fig. 4). The cranial sutures were separated. A diagnosis of craniopharyngioma was made and on the sixth hospital day craniotomy was done, utilizing a coronal scalp incision and a right frontal bone flap. A cyst was exposed behind the chiasm and on aspiration 15 c.c. of dark yellow, oily fluid were obtained. Because of the extent and location of the cyst, no attempt was made to remove it at this time. Twelve days later the bone flap was re-elevated and, employing a transventricular approach, a large portion of the cyst wall was removed from the third ventricle. Pathologic examination of the specimen showed it to be craniopharyngioma.



Fig. 4.—Roentgenogram of skull in Case 1. Note separated sutures and suprasellar calcification.

The child made an uneventful convalescence except for the development of diabetes insipidus of moderate severity. Her pressure symptoms were relieved entirely and she was discharged home on Sept. 30, 1941.

*Second Admission:* The patient was readmitted to The Children's Hospital on Feb. 23, 1942, because of recurrent headaches. In the five months at home there was progressive loss of appetite and she lost nine pounds. (Fig. 5.) The diabetes insipidus had persisted. She became increasingly weak and tired easily. In the two weeks prior to admission frontal headaches had returned without associated vomiting or visual disturbances.

Physical examination showed a bright, emaciated child with a well-healed coronal scar. Optic discs were quite normal in appearance with neither atrophy nor papilledema. Neurological examination was otherwise unchanged and visual fields remained full. Roentgenograms showed no evidence of intracranial hypertension but there was an increased amount of suprasellar calcification.

Basal metabolic rate was +8 per cent by weight and -13 per cent by height. Fasting blood sugar, 93 mg. per cent; blood chlorides, 114 milliequivalents per liter; sodium, 144 milliequivalents per liter; nonprotein nitrogen, 32 mg. per cent; serum protein, 7.2 Gm. per cent; glucose tolerance test showed a rather flat curve; and urine concentrated to a specific gravity of only 1.010.

Ventriculograms on March 5, 1942, showed considerable dilatation of each lateral ventricle with a large filling defect in the anterior part of the third ventricle. Craniotomy

was then immediately carried out and by transventricular exposure a large recurrence of the cyst was removed from the third ventricle.

The patient had an extremely stormy postoperative course characterized by stupor, swinging fever, and inability to take fluids orally, necessitating gavage feedings. She then embarked on a steady downhill trend illustrating the characteristics of pituitary 'cachexia

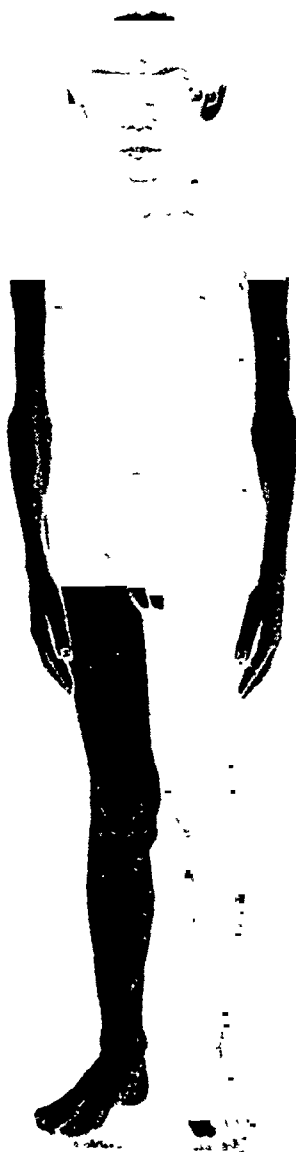


FIG. 5.—Case 1 (N. T.) at time of second hospital admission six months later. Early cachexia, complicated by severe disturbance of temperature regulation. She developed marked dehydration despite adequate fluid administration (Fig. 6) and was restored to transitory electrolyte equilibrium with the aid of adrenal gland extract therapy. Temporary improvement



in state of consciousness, appetite, and a gain of ten pounds despite discontinuance of substitution therapy occurred during the next two months. However, three months after the last operation she developed ventricular obstruction and again became comatose. One last operative attempt to relieve the obstruction was decided upon. Consequently, on June 9, 1942, the right frontal flap was elevated for the fourth time and again a large recurrence of cystic and solid tumor was removed from the third ventricle. Following the operation she developed a severe pneumonia and died fifteen days later.



Fig. 6.—Case 1 (N. T.) after development of severe pituitary cachexia two months later.



Fig. 7.—Case 1 (N. T.). Sagittal view of brain at autopsy with residual craniopharyngioma in situ.

Autopsy revealed severe emaciation with mild hirsutism and a generalized interstitial pneumonia. A partially solid craniopharyngioma had virtually destroyed the hypothalamus and the structure of the ventral thalamus (Fig. 7). No trace could be found of the tuber

cinereum, infundibulum, mammillary bodies, or hypophysial stalk. There was almost complete atrophy of the posterior part of the hypophysis and great diminution in size of the anterior lobe. The tumor was a craniopharyngioma of the simple squamous epithelial type.

CASE 2.—(A case of craniopharyngioma in a boy with several unusual features.)

A. S. (P. B. B. H. Surg. #78254). A 13-year-old boy was admitted to the Peter Bent Brigham Hospital on July 11, 1945, because of progressive loss of vision of eight months' duration. Past history and family history were noncontributory. Four years before admission the patient had the first of a series of "psychic seizures" which were all of a similar character. These episodes had a sudden onset and were characterized by mental confusion with a "rush of ideas" and were usually followed by a "dreamy state" lasting for two to three hours. These fugue-like spells were unaccompanied by any involuntary movements and occurred ten to fifteen times each year. Mild frontal headaches began to appear about two years before admission and for eight months there had been progressive loss of visual acuity. There were no other complaints. The patient had always been "slightly small for his age."



Fig. 8.—Case 2 (A. S.). Roentgenograms of skull with 40 c.c. air injected into residual cystic craniopharyngioma.

Physical examination revealed a rather thin, slightly undersized and underdeveloped 13-year-old male. Heart, lungs, and abdomen were normal. Visual acuity was 20/100 in each eye. Visual fields showed a classical right homonymous hemianopsia with some sparing of central vision. Fundi revealed rather severe optic atrophy on the right and 1 to 2 diopters of papilledema on the left. There was a right facial weakness of the supranuclear type. The remainder of the examination showed nothing abnormal.

Routine laboratory studies were within normal limits. Basal metabolic rate was -30 per cent.

Roentgenograms of the skull revealed increased convolutional markings with slight separation of the cranial sutures. The sella was normal except for atrophy of the posterior clinoids. There was marked thinning of the left temporal bone.

Preoperative diagnoses were: cystic astrocytoma, left temporal lobe; or craniopharyngioma with temporal lobe extension.

A left temporoparietal craniotomy was done on July 19, 1945. A cyst wall was encountered about 2 mm. below the surface of the second left temporal convolution. This was tapped with the removal of about 120 c.c. of clear dark yellow fluid containing cholesterol crystals. The collapsed cyst was then dissected free from the surrounding brain tissue and excised at its base which was found to consist of solid tumor densely adherent to the region of the sella turcica. Pathologic report was craniopharyngioma.

The patient made a smooth postoperative recovery except for a transitory third nerve weakness which had largely returned to normal at the time of discharge.

Three thousand roentgens of irradiation were given in an effort to reduce the tendency to recurrence. Following the roentgen therapy the cyst was tapped through a decompression in the bone flap and 40 c.c. of cyst fluid could be withdrawn and replaced by air, following which roentgenograms were taken to delineate the size and location of the remaining cyst. (Fig. 8.) The patient was discharged home on Aug. 11, 1945. Since his discharge from the hospital he has returned to school and has led an essentially normal life. When last seen, five months after discharge, there was a persistence of hemianopsia but visual acuity was 20/30, and there was no evidence of increased intracranial pressure.

We propose to continue treatment by aspiration of the cyst, resuming roentgen therapy when symptoms reappear.

With these two case reports to illustrate the complex problems which may arise, the more general principles involved may be considered.

#### PATHOLOGY

Along the anterior aspect of the stalk of otherwise normal pituitaries there are found remnants of the hypophysial duct persisting as islands of squamous epithelium. Neoplastic proliferation of these cells results in the formation of squamous epithelial cysts. These occur most commonly along the pituitary stalk at the level of or above the diaphragma sellae. This accounts for the fact that the anatomic term "suprasellar cyst" has been so frequently used in describing these tumors.

Hypophysial duct tumors are almost invariably cystic, but many of them possess solid portions consisting of masses of squamous epithelium in which calcification frequently occurs. These calcareous masses are likely to lie at the base of the lesion representing the point of attachment of the cyst and its source of blood supply. There is a good deal of variation in the size and gross appearance of these neoplasms. From tiny thin-walled cysts located behind the optic chiasm they may range to huge, complex multiloculated cystic and solid masses which fill and distend the third ventricle, extending upward into the frontal lobes and backward through the interpeduncular fossa against the brain stem.

In the larger cysts the capsule has a smooth, gray-white external appearance, and a fairly tough consistency. The cyst's contents which are composed of desquamated and liquefied squamous epithelial debris, usually consist of an oily brown or golden-yellow fluid resembling motor oil. Floating on the surface and suspended in the fluid one may readily observe numerous glistening

cholesterol crystals. There may be varying amounts of grumous material representing unliquefied epithelial detritus. If the cyst wall is thin, its external surface may be a dark brown or have a bluish hue as a result of the color of the contained fluid.

The lining of most craniobuccal cysts is granular and rough as the result of proliferation of squamous cells with formation of papillary excrescences which frequently undergo keratinization and calcification (Fig. 9).



Fig. 9.—Sagittal section of brain of a child with a huge craniopharyngioma. Note smaller solid tumor and superimposed cyst with flecks of calcium in its wall.

There is as much histologic variation in these tumors as there is variety in their gross appearance. This has led to considerable confusion in classification and terminology. Since tumors of the hypophysial duct arise from cell rests of buccal ectoderm they are potentially able to reproduce the various elements of the buccal cavity. Hence it is not surprising that some pathologists have emphasized the resemblance of certain of these tumors to the adamantinomas or ameloblastomas of the jaw. Bailey<sup>11</sup> recognizes three histologic types of tumor having origin in remnants of the hypophysial duct: mucoid epithelial cysts, adamantinomas, and simple squamous epitheliomas.

The mucoid epithelial cysts which he describes are lined by columnar ciliated epithelium and are thought to take origin in Rathke's cleft (hypophysial cleft). Examples of these rare cysts are described by Duffy<sup>2</sup> and by Frazier and Alpers.<sup>12</sup> This type of cyst did not occur in any of our patients.

The adamantinomatous type of craniopharyngioma, according to Bailey,<sup>11</sup> is characterized by the presence of a row of columnar cells arranged in palisade formation next to the connective tissue resembling the adamantoblasts or ameloblasts of tooth-buds. Critchley and Ironside,<sup>3</sup> Peet,<sup>13</sup> Frazier and Alpers,<sup>6</sup> and

others apparently feel that tumors of the hypophysial duct (as opposed to the mucoid epithelial cysts which are presumably tumors of the hypophysial cleft) should be classified as adamantinomas or ameloblastomas. In this group of sixteen cases only one tumor showed histologic structure suggestive of the adamantinoma of the jaw. In the remaining fifteen cases there were tumors which belonged in Bailey's classification of simple squamous epitheliomas.

The essential histologic structure in this common type is that of masses and anastomosing cords of squamous epithelium lying in a stroma of fibrous connective tissue (Fig. 10). The epithelium resembles that of the skin. It is stratified squamous in type, some of the cells having intercellular bridges. The



Fig. 10.—Photomicrographs of craniopharyngioma of the simple squamous epithelial type. Note calcification (upper right).

cells nearest the lumen of the cyst undergo keratinization. There is frequently an outer layer of cylindrical cells with central stratification, flattening, and keratinization or cyst formation. The lining of the larger cysts consists of flattened squamous epithelium which is occasionally proliferated so as to form papillae. Calcification is occasionally present in the central area of these papillae. Irregular slits and clefts in the fixed sections are presumed to represent the site of cholesterol crystals. In one of our specimens there was metaplastic bone formation adjacent to the calcified area. The solid masses of the craniopharyngiomas are usually separated from neighboring brain or hypophyseal tissue by only a thin layer of gliosis and possess no well-defined capsule. The larger cysts, however, quite frequently have a tough fibrous capsule, which may be continuous with the dura at the base. This capsule is probably derived from the tumor's connective tissue stroma.

No evidence of malignant change was encountered in the specimens removed at operation or in any of the autopsy material. Reports in the literature of carcinomatous types of craniopharyngiomas are difficult to assess because of the frequency with which nasopharyngeal cancer invades the hypophyseal region. Peet,<sup>13</sup> however, reported one case in a child of undoubted carcinomatous features developing in an adamantinomatous craniopharyngioma.

*Pathologic Physiology.*—The common location of craniopharyngiomas in the region of the stalk of the hypophysis makes possible severe physiologic disturbances as a result of the compression of adjacent structures. These disturbances may be grouped under four headings: visual disturbances, intracranial hypertension, hypophyseal disorders, and hypothalamic disorders.

The optic chiasm may be compressed from below or above, depending upon the tumor's origin being below or above the diaphragma sellae. Since the most frequent location of the tumor is suprasellar, the chiasm is most commonly pushed downward and forward with production of lower quadrant field defects in the early stages and, later, bitemporal hemianopsia. As the growth of the tumor is frequently asymmetrical, a right or left homonymous hemianopsia may result from optic tract damage. The less common intrasellar or subchiasmal types of the lesion, usually expand anteriorly, rupturing the diaphragma and pressing upward on the chiasm or extending in front of it. Bizarre types of visual field defects, therefore, may be expected from these tumors. However, in some cases there may be no detectable field defects despite the presence of a suprasellar cyst. Primary optic atrophy with early loss of vision may be produced as the result of compression of the optic pathways in the chiasmal region.

Ventricular obstruction may develop when the larger cystic expansions of the tumor extend upward, invaginate the floor of the third ventricle, and either fill the anterior portion of the ventricle or block one of the interventricular foramina. This is extremely common in craniopharyngiomas in children and the acute hydrocephalus which results accounts for the symptoms of intracranial hypertension and subsequent separation of the cranial sutures.

The larger cysts occasionally rupture and spill their highly irritating contents into the ventricular system or subarachnoid space. This results in a severe aseptic ventriculitis and meningitis.

Disturbance of hypophysial function probably occurs in greater or lesser degree in all patients with craniopharyngiomas. In children, probably the most common clinical manifestation of hypophysial deficiency in association with these tumors, is arrested skeletal development. The more severe degrees of anterior lobe deficiency produce the so-called Lorain type of dwarfism with associated sexual infantilism. Pituitary cachexia of the Simmond type is much less common with craniopharyngiomas but was present in two of the children in the group under discussion. Hyperpituitary states such as gigantism, acromegaly, and basophilism are not produced by these tumors. Diabetes insipidus is fairly common in children with craniopharyngiomas and is attributed to damage to the supraoptic nuclei or the supraopticohypophysial tract in the pituitary stalk.

The extension of craniopharyngiomas upward with invagination of the floor of the third ventricle results in compression of the hypothalamic nuclei lying in the floor and walls of the ventricle. More or less destruction of parts of the hypothalamus may result, while varying degrees of stimulation of remaining hypothalamic nuclei may occur simultaneously in the same individual. Bizarre disturbances of hypothalamic function may be produced.

Fulton<sup>14</sup> recognizes five clinical syndromes of the hypothalamus: (1) hypothermia (from damage to the posterior nuclei); (2) hypersomnia (posterior nuclei and mammillary bodies); (3) adiposogenital syndrome of Fröhlich with disturbed fat and carbohydrate metabolism (tuber cinereum); (4) diabetes insipidus (supraoptic nuclei) generally accompanied by hyperthermia; and (5) autonomic epilepsy with manifestations varying with the site of the lesion and presenting a mixture of sympathetic and parasympathetic reactions.

Since the functions of the hypophysis and of the hypothalamus are so closely interrelated and since craniopharyngiomas frequently cause compression of both centers, the clinical syndromes encountered with these tumors can rarely be attributed to individual disturbance of either. More frequently they present features resulting from disturbances of both hypophysis and hypothalamus.

#### CLINICAL ASPECTS

A. *Incidence.*—In Cushing's<sup>1</sup> series of 2,000 verified intracranial tumors, craniopharyngiomas comprised 4.6 per cent of the total. The age distribution in his group of 92 craniopharyngiomas at the time of symptomatic onset showed 14 for the first decade, 29 for the second, 19 for the third, 13 for the fourth, 9 for the fifth, 6 for the sixth, and 2 patients were over 60 years of age. His youngest patient was 3½ years old.

At The Children's Hospital, 190 intracranial tumors have been verified during the thirteen-year period of 1933 to 1945, inclusive. Twelve of these tumors were craniopharyngiomas, an incidence of 6.3 per cent of the intracranial tumors in children under 15 years of age in a general pediatric clinic. The youngest patient with a craniopharyngioma was 4 years of age, and the oldest was 13 years of age.

The sexes were equally distributed in this group of patients, although some reports in the literature suggest a slight male predominance. There was no indication of any familial incidence in this group of children.



Fig. 11.—Surgical intervention was required by this patient for relief of increased intracranial pressure four times in a period of four years. Note moderate weight increase during this time.

B. *Symptoms.*—The most common initial symptoms of craniopharyngioma in these patients were headache and vomiting, occurring in 15 of the 16 children. This differs markedly from the early symptomatology of this tumor in adults who are more likely to have visual disturbances as a mode of onset, with manifestations of intracranial hypertension as a relatively late occurrence.



Progressive loss of vision occurred in 9 children, 2 of whom were totally blind at the time of hospitalization.

Arrested growth was the third most frequent complaint, being encountered in 5 children. Actual weight loss occurred in 4 children, and progressed to a severe degree of cachexia by the time of admission in one instance (Fig. 5).

Diabetes insipidus had developed in 3 children before hospitalization. This symptom was more commonly encountered as a transitory sequel to operation.

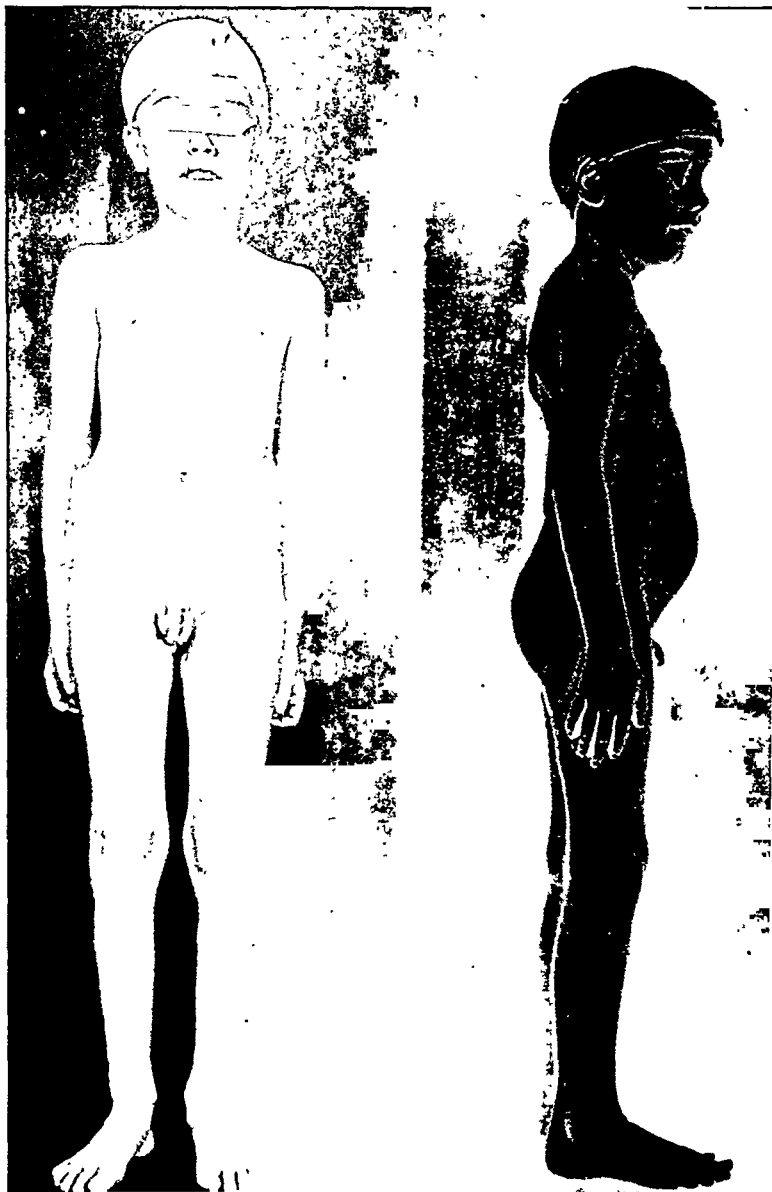


Fig. 12.—Twelve-year-old boy with craniopharyngioma. There had been no apparent growth for four years.

One child had mild convulsive seizures, another had attacks of syncope, and a third had a staggering gait with definite cerebellar ataxia. "Dreamy states" and fugue-like episodes were encountered in the 13-year-old boy (Case 2) whose tumor extended into the left temporal lobe.



Fig. 13.—Photograph of an 8½-year-old girl with craniopharyngioma taken at time of initial hospitalization. Patient had severe cachexia and was in coma on arrival.

Fröhlich's syndrome (*dystrophia adiposogenitalis*), which has been emphasized in several reports as being the common clinical picture of craniopharyngiomas in children, was not encountered among the patients although one girl showed moderate weight gain during the course of treatment (Fig. 11).

In general, the presenting symptomatology of craniopharyngiomas in this group of children at the time of initial hospitalization was characterized by intracranial hypertension as manifested by headache and vomiting associated with progressive visual loss in more than one-half, arrested skeletal development in less than one-third, and uncommonly, with diabetes insipidus and the overt forms of hypothalamic disorders.

C. *Signs.*—The most consistently positive physical findings in our experience in children with craniopharyngiomas are met in examination of the ocular fundi and the visual fields. Changes in the optic discs on ophthalmoscopic examination were encountered in all of the 16 patients. Bilateral primary optic atrophy was present in 7 children when first studied, while 5 others had bilateral papilledema. Swelling of the nerve heads, bilaterally, combined with abnormal pallor was observed in two individuals. The 2 remaining children showed the fundoscopic changes of the Foster Kennedy syndrome, namely, papilledema in one eye and optic atrophy in the other.

Visual field determinations were carried out on admission in 13 of the 16 children. Fields could not be measured in two instances because of total blindness, and in the case of another child who was brought to the hospital in coma, they were necessarily omitted.

Essentially normal visual fields were found in 5 instances. In 5 others, bitemporal hemianopsia or bitemporal quadrantic defects were present. One child whose cyst had expanded into the left temporal lobe showed a right homonymous hemianopsia. Two other children had lost all vision in the field of one eye and had temporal defects in the other eye field.

Five children were definitely undersize. One 12-year-old boy had shown no growth in the four years preceding admission (Fig. 12). An 8-year-old girl who was admitted in coma showed severe cachexia of the Simmond type (Fig. 13). The other ten children were essentially normal in size, development, and physical appearance.

Macewen's sign (cracked-pot resonance) on percussion of the skull was elicited in 5 children in whom separated sutures were later disclosed by x-ray.

Other abnormalities on neurological examination were strikingly rare in this group of children. Three patients had convergent squint as a result of lateral rectus weakness from sixth nerve palsy. Two others showed a mild hemiparesis with facial weakness of the supranuclear type. Ataxia was present in 2 individuals, leading to a mistaken diagnosis of cerebellar tumor and ultimate suboccipital exploration in one case. In 9 children no neurological changes were elicited other than those disclosed on examination of visual fields and fundi.

Most of these children were mentally alert and in some cases considered to be intellectually precocious.

The systolic blood pressure tended to be normal or slightly subnormal in all of these patients despite the associated intracranial hypertension.

D. *Laboratory Findings.*—Routine laboratory studies of blood and urine at the time of hospitalization were essentially normal in these 16 children,

with the exception of low specific gravity of the urine in the 3 patients with diabetes insipidus. Fasting blood sugar levels were determined in 13 individuals and were within the normal range (90 to 110 mg. per cent) in 10 children, and only slightly low (70 to 90 mg. per cent) in 3 others. Glucose tolerance tests showed a normal curve in 6 patients, and were not carried out in the remainder of the group. The basal metabolic rate was low (below -10 per cent) in 5 children, normal in 2, and not determined in the others prior to operation.

Determinations of 17-ketosteroids and blood iodine were not made in any of the patients before operation was performed. A lowered metabolic rate, associated with a reduced blood iodine level and depressed 17-ketosteroid excretion is indicative of anterior pituitary deficiency in these children. Such studies are probably more valuable in following the course of the disease than in establishing a diagnosis of craniopharyngioma.

*E. Roentgen Findings.*—Roentgenograms of the skull showed definite abnormalities in all the patients with craniopharyngiomas. Calcification above the sella turcica was present in 8 cases, and intrasellar calcification appeared in 2 others. This invaluable finding, which McKenzie and Sosman<sup>15</sup> observed in 71 per cent of craniopharyngiomas in Dr. Cushing's series, is almost pathognomonic of the tumor in children. The visible calcification is most often present in the solid, basal portion of the tumor, appearing in the roentgenogram as a collection of delicate, spongy flecks of opacity (Fig. 4). Rarely, there may be large masses of calcium and, still more rarely, part of the cyst wall may be outlined by calcification.

Roentgenologic evidence of increased intracranial pressure as indicated by separated sutures, convolutional atrophy, or erosion of the clinoid processes, was observed in 7 children. The sella turcica was enlarged and distorted in one-half of the cases. Usually, the enlargement of the fossa is of an irregular type with depression of the floor and is associated with erosion of the dorsum sellae or posterior clinoid processes (Fig. 14).

Significant retardation of bone age, as estimated by examining x-rays of the wrists, was encountered in 5 of this group of children when first seen.

*F. Differential Diagnosis.*—With a history of failing vision, headaches and vomiting, and the finding of calcification in or above the sella turcica on roentgen examination, a diagnosis of craniopharyngioma can usually be made unequivocally in children. Although dermoid cysts, chordomas, and teratomas may occur in the vicinity of the sella, they are much less common and are not likely to show the delicate flecks of calcification so characteristic of the craniopharyngioma. In 10 of these patients no diagnostic difficulties were encountered because of this association of findings.

In those instances in which a chiasmal syndrome is encountered in a child with enlargement of the sella but without calcification, the age of the patient is of considerable aid in excluding pituitary adenoma, as adenomas are extraordinarily rare in childhood. In Dr. Cushing's series of 338 pituitary adenomas, there were only 3 patients under the age of 18, the youngest being

10 years of age.<sup>16</sup> At The Children's Hospital we have seen only 2 children with adenomas in the last 15 years.

In the absence of both calcification and enlargement of the sella, a child with evidence of intracranial hypertension and a chiasmal syndrome presents a more difficult problem in diagnosis. Gliomas of the optic nerves and chiasm usually produce rapid loss of vision and the optic foramina are frequently enlarged on roentgen examination. Tumors of the third ventricle, such as teratomas, colloid cysts, hamartomas, and gliomas, must be considered and ventriculography is usually indicated to clarify the issue in such instances. In spite of this aid it may be impossible to make an accurate diagnosis preoperatively.

Ataxia, which may result from extension of craniopharyngiomas into the interpeduncular fossa and through the incisura tentorii, was described by Bailey.<sup>17</sup> This was so marked in one of our patients that a diagnosis of cerebellar tumor was made and suboccipital exploration performed.



Fig. 14.—Roentgenogram of skull of 7 $\frac{3}{4}$ -year-old girl with craniopharyngioma. Note huge, distorted sella.

Aneurysms of the circle of Willis, and meningiomas of the tuberculum sellae are important in the differential diagnosis of craniopharyngiomas in adults, but are quite unlikely to appear in childhood.

Internal hydrocephalus from any cause, with dilatation of the third ventricle, may occasionally simulate craniopharyngioma in producing chiasmal

signs and erosion of the clinoid processes. The hypothalamic disturbances of a functional nature and the residue of certain of the encephalitides must also occasionally be given consideration.

#### TREATMENT AND RESULTS

The benign histologic nature of craniopharyngiomas would tend to suggest that complete surgical removal should result in cure. Unfortunately, the environmental relationships of the tumor are such that total removal can rarely be accomplished without the loss of the patient's life. Attempts at radical excision have not infrequently resulted in immediate or early post-operative death from disturbance of hypothalamic function. Conservative operative intervention with evacuation of the cyst and partial removal of the wall has often provided relief from symptoms for a period of years, and has undoubtedly preserved vision in many patients who have survived for varying lengths of time.

Details of operative technique need not be given in this communication. In general we have found a coronal scalp incision the most satisfactory. With the scalp reflected anteriorly, a small right frontal bone flap is turned down and the region of the optic chiasm exposed by retracting the right frontal lobe either intradurally or extradurally. If the lesion cannot be exposed in this way, a transventricular approach can be made by traversing the right frontal pole. It may then be possible to reach the cyst through the right foramen of Monro, evacuate its contents, and remove a portion of the wall. If exploration suggests that a more extensive removal might be advantageously accomplished by a more complete exposure, a left frontal bone flap may be added, the longitudinal sinus and falx divided, and the tumor exposed through incision of the corpus callosum into the third ventricle. The use of this radical approach has seldom been indicated in this series of cases, but on three occasions has proved to be very satisfactory.

The management of those rare instances in which a large cystic craniopharyngioma ruptures into the ventricular system or subarachnoid space entails institution of drainage of ventricular and spinal fluid as an emergency measure. These episodes are characterized by an abrupt change in symptoms with rapid development of signs of meningeal irritation and usually coma. Repeated taps and continuous spinal drainage are necessary in order to remove the extremely irritating cyst contents from the cerebrospinal fluid pathways.

The availability of whole adrenal gland extracts has simplified, somewhat, the care of these patients during the most critical period. By the use of adrenal cortical extracts, the marked fall in blood pressure and tendency to collapse as the secondary results of pituitary disturbance before, during, and after operation, have been successfully dealt with.

Roentgen therapy of these cystic tumors was suggested by Frazier and associates in 1937, at a time when the results of surgical attack seemed unpromising. He and his associates<sup>18</sup> reported four patients (in three of whom the diagnosis had been verified histologically) who improved to a greater extent following surgery and radiation than would have been expected from

surgical treatment alone. Davidoff<sup>19</sup> is of the opinion that certain of the craniopharyngiomas respond well to radiation therapy, although it is impossible to predict which patients may be so benefited. He has recently had the following rather convincing experience: A patient with a proved craniopharyngioma was treated by operation consisting of evacuation of the cyst and partial removal of the wall, followed by radiation. Complete relief of symptoms was obtained for a period of two years. Recurrence at that time was checked by a second course of radiation.

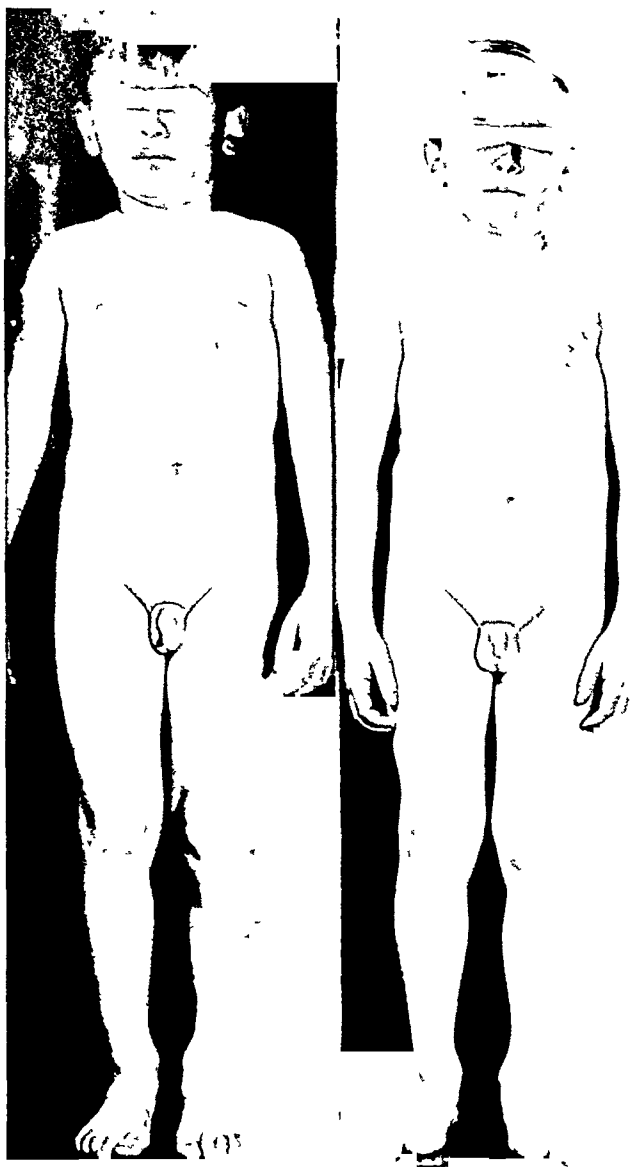


Fig. 15.—Photographs of patient who has survived thirteen years following partial removal of craniopharyngioma. At left, aged twelve years (height 47½ inches, weight 53 pounds); and at right, aged 16 years (height 51 inches, weight 77 pounds).

It has been assumed that the solid portion of the tumor has not been appreciably affected by irradiation but that the cells producing the fluid may have had their secretory character altered. Although many neurosurgeons are of the opinion that radiation of these lesions is quite useless, there would seem to be sufficient evidence to warrant further trial with critical evaluation of results. It should be pointed out that the issue would not be clarified and the patient might suffer loss of visual function if the radiation were carried out without biopsy.

All of the patients were subjected to surgical exposure of the cyst by transfrontal craniotomy with aspiration of contents and removal of as much cyst wall as was readily available in each instance.

Five children are now alive in this group of 16 patients with craniopharyngiomas—a survival rate of 31 per cent. Only 2 of these can be considered “cures” from the standpoint of significant survival. One boy, although retarded in growth, has normal vision and has lived for thirteen years without evidence of recurrence since the partial removal of the cyst (Fig. 15). The other patient, also a boy, is totally blind but has had no return of symptoms for ten years. Less than a year has elapsed since operation on the 3 remaining children.

All the 11 children who died succumbed to the late effects of the tumor or to the direct complications of operative treatment. Repeated operative attacks on the tumor for recurrence of symptoms were carried out in 7 of these patients and 3 children were subjected to as many as four craniotomies in an effort to check the progress of the tumor.

#### COMMENT

Despite the rather discouraging results obtained by surgical treatment in this group of patients, there is no other logical approach to the problem presented by craniopharyngiomas. A well-planned exposure with aspiration of the cyst and partial removal of its wall can be carried out without mortality in most cases. The diagnosis can thus be verified and symptoms alleviated, albeit only temporarily. There was only one postoperative death following the 16 initial craniotomies in this group of children, and in that instance extensive removal of a solid portion of the tumor had been undertaken. Impending blindness may be forestalled by this relatively simple procedure and in some unusually fortunate cases there may be no return of symptoms for surprisingly long periods of time. Six children treated in this manner showed no evidence of recurrence for periods of one year or longer, and one of these cases has shown no progression of symptoms for thirteen years.

By far the majority of the cases have had recurrence of symptoms in the first three to six months after operation. Some of these children have shown progressive blindness, somnolence, anorexia, cachexia, temperature irregularities, and a few have reached a decerebrate state before exitus. More of them have simply developed return of the symptoms of intracranial hypertension as evidence of refilling of the cyst. Repeated surgical attacks on the tumor have in a few instances prolonged the survival period five or six years, but



the majority of individuals with early recurrence have succumbed in the first eighteen months after the initial operation, despite multiple operative procedures.

In general, it seems logical to conclude that the patients with late recurrence, who have had a relatively long remission following partial removal of the cyst, should be subjected to a repetition of surgical treatment, whereas those with early recurrences and without contraindication such as serious reduction of visual acuity, might best be treated by withholding surgery and instituting roentgen therapy. Our experience with irradiation, in these instances, is too limited to warrant any conclusions, but on the basis of that of Davidoff and others we feel that this plan should be followed until more nearly complete appraisal has been made.

It should be emphasized that most of these children were brought to the hospital for initial treatment only after severe symptoms had developed as the result of cystic tumors of considerable size. By careful study including examination of visual fields and ocular fundi, and careful interpretation of roentgenograms of the skull, it should be possible to recognize craniopharyngiomas in children long before impending blindness, pituitary cachexia, separated cranial sutures, or coma make hospitalization a desperate emergency procedure.

#### SUMMARY

1. Experience with 16 craniopharyngiomas in children observed at The Children's Hospital and the Peter Bent Brigham Hospital, Boston, during the period of 1933 to 1945, is reported.

2. Two cases are presented in detailed reports.

3. Embryologic, pathologic, physiologic, diagnostic, and therapeutic aspects of craniopharyngiomas in children are discussed.

4. It is suggested that a critical appraisal be made of roentgen therapy as an adjunct to surgery in the management of these tumors.

#### REFERENCES

1. Cushing, Harvey: *Intracranial Tumors*, Springfield, Ill., 1932, Charles C. Thomas, Publisher, p. 93, 102.
2. Duffy, W. C.: *Ann. Surg.* 72: 537, 725, 1920.
3. Critchley, M., and Ironside, R. N.: *Brain* 49: 437, 1926.
4. McLean, A. J.: *Ztschr. f. d. ges. Neurol. u. Psychiat.* 126: 639, 1930.
5. Beckmann, J. W., and Kubie, L. S.: *Brain* 52: 127, 1929.
6. Frazier, C. H., and Alpers, B. J.: *Arch. Neurol. & Psychiat.* 26: 905, 1931.
7. Love, J. G., Sheldon, C. H., and Kernohan, J. W.: *Arch. Surg.* 39: 28, 1939.
8. Mott, F. W., and Barrett, J. O.: *Arch. Neurol. & Psycho-Path.* 1: 417, 1899.
9. Erdheim, J.: *Sitzungsbd. d. Akad. d. Wissensch.* 113: 537, 1904.
10. Bremer, J. L.: Personal communication.
11. Bailey, Percival: *Tumors of the Hypophysis Cerebri*, in *Penfield's Cytology and Cellular Pathology of the Nervous System*, New York, 1932, Paul B. Hoeber, Inc., Vol. 3, p. 1133.
12. Frazier, C. H., and Alpers, B. J.: *Arch. Neurol. & Psychiat.* 32: 973, 1934.
13. Peet, M. M.: *Arch. Surg.* 15: 829, 1927; *Warthin Ann.* Vol. 673, 1927.
14. Fulton, J. F.: *Physiology of the Nervous System*, ed. 2, New York, 1943, Oxford University Press.
15. McKenzie, K. G., and Sosman, M. C.: *Am. J. Roentgenol.* 11: 171, 1924.
16. Henderson, W. R.: *Brit. J. Surg.* 26: 811, 1939.
17. Bailey, Percival: *Arch. Neurol. & Psychiat.* 11: 137, 1924.
18. Carpenter, R. C., Chamberlin, G. W., and Frazier, C. H.: *Am. J. Roentgenol.* 38: 162, 1937.
19. Davidoff, Leo: Personal communication.

# The Academy Study of Child Health Services

On May 24, 1946, the Executive Staff of the Study met with the Advisory Committee in order to discuss plans for the analyses and tabulation of data now being collected in the states throughout the country. Dr. Warren R. Sisson, Chairman of the Academy Committee for the Study of Child Health Services attended this meeting.

The discussion was of a preliminary nature and was concerned with plans for the tabulation and analyses of data to determine the availability and receipt of medical care and health services for children in communities or areas of varying geographic, economic, and sociologic character. It was accepted that these plans might be subject to revision as the Study progresses. However, it is appropriate at the present time to publish these discussions for the information of the Academy membership which is fulfilling with notable success its grave responsibility in this enormous undertaking.

In general, the Study of Child Health Services may be divided into three steps: (1) collection of data, (2) tabulation and analyses of the data, (3) preparation of the reports. With the Study programs well underway in 38 states, and all but five states showing some degree of activity, the first step is progressing rapidly. Returns from North Carolina where the pilot study has been conducted are well in hand, with members of the field staff from the Central Office completing the final details in that State. Plans for the tabulation of the results of the pilot study and of subsequent state studies have been under consideration for some time. At this stage it was considered necessary to make some basic decisions as to the handling of the data.

One of the first considerations was to determine the basic classification by which the data are to be tabulated. Inasmuch as the data will be broken down on a county, and where advisable, a city basis, the first problem was to set up the procedure for classification of the counties. Material for the Study is collected by counties because health records are established and maintained on this basis. But counties are political units, and not necessarily comparable geographic or population units. Some are large, some small; some are densely populated, some have few inhabitants; some have high per capita income, some very low. Moreover, listing of facilities available in the more than 3,000 counties of the country would have little meaning. Hence some method of grouping counties with similar traits became necessary.

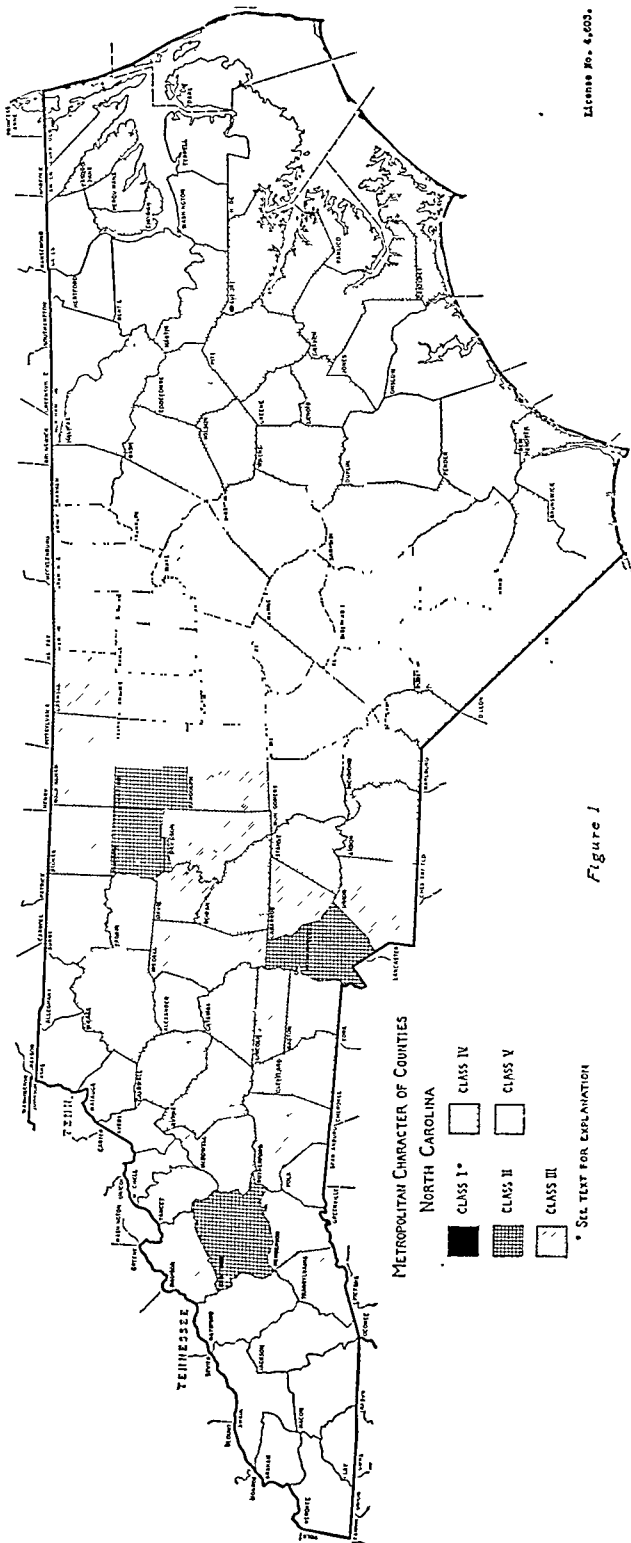
Three methods of grouping were discussed: (1) metropolitan character of the county, (2) largest urban community in the county, and (3) per capital buying power. Maps of five typical states were prepared on each of these three bases and tables drawn up using already available data to demonstrate to the committee the comparative usefulness of the three methods considered. The Metropolitan character of county method\* was selected by the Committee.

A metropolitan county is defined as: (a) one containing a city of 50,000 or more inhabitants, or (b) one adjacent to such county containing a densely populated area of 150 or more persons per square mile in any bordering township. A division of these counties was made by separating those with districts of a million or more people to form a super metropolitan group (Class I).† All other metropolitan counties fall into Class II.

The remaining counties in any state cannot be indiscriminately grouped together as non-metropolitan, because obviously those counties adjacent to large cities have more readily available health facilities and services than others further removed. Therefore, for purposes of classification, all counties geographically adjacent to metropolitan counties are grouped un-

\*This classification is based upon one used by the United States Census Bureau, and has been modified and amended by the staff of the Study of Child Health Services with the help and advice of Mr. Elliott H. Pennell, Chief, Statistical Section, States Relation Division, United States Public Health Service.

†Baltimore, Boston, Chicago, Cleveland, Detroit, Los Angeles, New York, Philadelphia, Pittsburgh, St. Louis, San Francisco.



License No. 4,603.

Figure 1

der the title of "First Tier (Class III). The counties on the outer circuit, those at the greatest distance from the metropolitan counties, are called Second Tier, and are subdivided into: (a) those containing incorporated places of 2,500 or more inhabitants (Class IV); and, (b) those containing no incorporated place of 2,500 population (Class V). Table I lists this basic stub, as it is termed, which will be used in analyzing a variety of facilities and services for child health at both the National and State levels.

TABLE I

TABLE 1

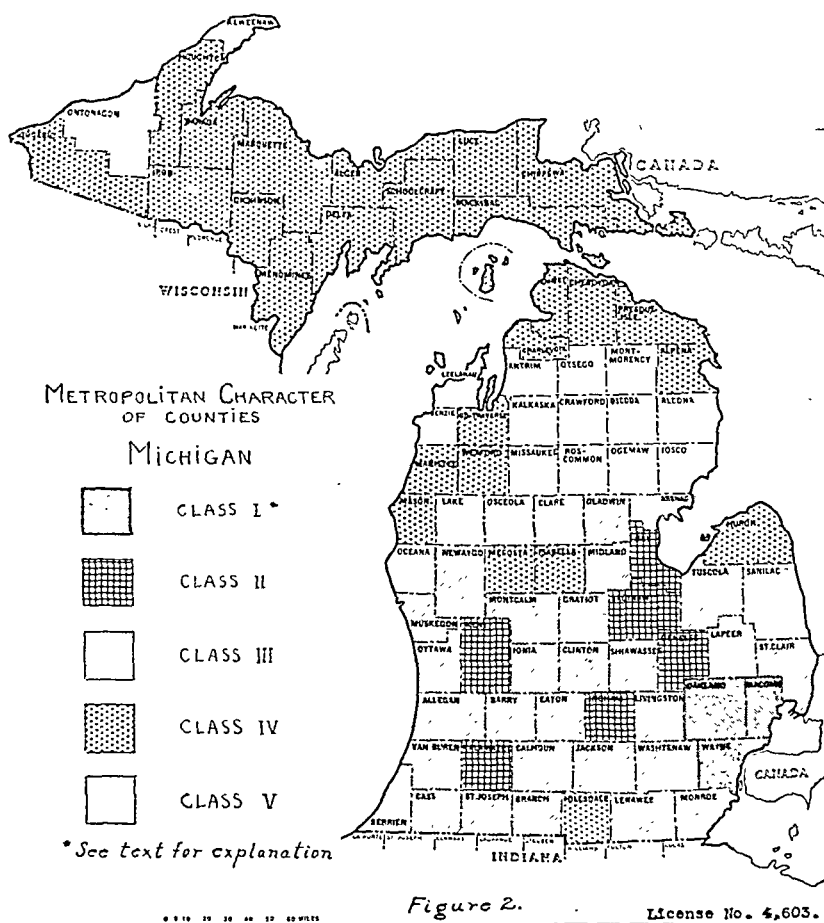
METROPOLITAN CHARACTER OF COUNTY	NO. OF PHYSI- CIANS IN PRIVATE PRACTICE	NO. OF PHYSICIANS SEE- ING CHILDREN	NUMBER OF VISITS PER DAY, BY AGE OF PATIENTS						PERSONS 15 OR MORE YR.
			ALL AGES	CHILDREN UNDER 15					
				ALL	UNDER 1 MO.	1 MO.- 1 YR.	1-5 YR.	6-14 YR.	
General Practitioners									
Class I									
II									
III									
IV									
V									
Pediatricians									
Class I									
II									
III									
IV									
V									
Other Specialists									
Class I									
II									
III									
IV									
V									

5/22/46

6/7/46

To illustrate this classification method, maps of North Carolina (Fig. 1) and Michigan (Fig. 2) are included. It will be noted that North Carolina possesses five counties described as metropolitan (Class II) each containing a city of 50,000 or more inhabitants. North Carolina has no Class I counties. Twenty-six counties are classified as First Tier (Class III), all being adjacent to metropolitan counties. For example, Buncombe County in the western part of the State is metropolitan in character because it contains the city of Asheville (population 51,320); whereas the surrounding or contiguous counties are First Tier by reason of their accessibility to a metropolitan area and its medical facilities. Progressing outward from the centers of population, thirty-three counties described as Second Tier (Class IV) and thirty-six Second Tier Class V) are found scattered throughout the State, the former including within their borders at least one incorporated town or place of 2,500 or more inhabitants, the latter being without any communities of this size. In this way, accessibility to medical facilities, which for the most part are located in larger communities, is graphically demonstrated for every part of the State. In addition, as a further check, it is planned to study road maps showing highways and secondary roads and other transportation routes to determine the accessibility of Class III counties to metropolitan areas.

A map of Michigan (Fig. 2) is presented to illustrate a state containing three Class I counties as well as several Class II counties. Certain other counties in Michigan, though lacking a city of 50,000 or more persons, are considered metropolitan because of other characteristics as already defined. It will be noted that Wayne, Oakland, and Macomb Counties are classified as metropolitan (Class I) by virtue of the fact that they each include part of



the metropolitan district of the city of Detroit (population 1,623,452).<sup>\*</sup> Saginaw County is metropolitan in character because its county seat, Saginaw, has a population of 82,794.<sup>\*</sup> Likewise, Bay County is considered metropolitan even though its largest urban community, Bay City, has a population less than 50,000. However, Bay County is adjacent to Saginaw County and contains one or more areas with a density of population of 150 persons per square mile in townships adjacent to Saginaw County.

The committee considered also the forms which the basic tables should assume. Illustrative table forms were presented to demonstrate the methods by which data from the various schedules might be tabulated using the county classification system as the basic stub. Samples of fifteen table forms, similar to Table I, based on material from Schedule III-A were exhibited and discussed in detail.

Certain technical items were also discussed such as ways and means of determining whether returns from physicians and dentists represent a reliable sample for estimating total community professional services for children.

The meeting closed with a brief discussion of the nature and amount of material to be returned to the states. The Academy is committed, not only to the task of preparing a report at the National level including tables showing data at the State level, but also to returning to the states tabular material broken down to the level of counties and large metropolitan areas. It was finally decided that the raw data, without attempts at interpretation, should be given back to each state for study and preparation of individual state reports.

<sup>\*</sup>Sixteenth Census of the United States, 1940. Vol. II.

# The Social Aspects of Medicine

WAGNER-MURRAY-DINGELL BILL (S. 1050)

Dear Dr. Park:

Senate Bill 1606 is now being given hearings in Washington. This is a modification of the earlier Wagner-Murray-Dingell bill (S. 1050) and is known as the "National Health Act of 1945." This draft differs fundamentally from other versions in that it eliminates (1) the provision dealing with the construction of hospitals and health centers, which is covered in the revised Hill bill (S. 191), and (2) provisions for financing Title II which must be provided in separate legislation. It deals in Title I with: A. Grants to states for public health services. B. Grants to states for maternal and child health services. C. Grants to states for medical care of needy persons; in Title II prepaid personal health service benefits.

Title IA requires no comments as there is quite general agreement in its support.

Title IB. Discussion of the matters contained in this section has been extensive since it follows in general the provisions of the Pepper bill (S. 1318). There is some advantage in having services for children included in the general health plan rather than considered as an independent service.

Title IC. Provides that the states shall determine the "need for medical care." This section sets up a system of medical care for the needy different from that for the rest of the population covered in Title II. It would seem better if the two systems could be combined into a single uniform plan by bringing the needy within the provisions of Title II. Cash benefits for medical care are provided and this is surely undesirable.

Title II provides for a National Insurance System. One's attitude toward this specific piece of proposed legislation is determined in large measure by his concept of government and its function in the social order. Those whose philosophy is based upon security as an ultimate goal will favor a maximum participation of government in community activities. Those who believe in individual responsibility and independence will strive less for security than for freedom and will scrutinize critically any extension of government participation in and control of local affairs. Everyone is agreed upon the desirability of the objective which this title aims to attain—namely better medical care for all the people in the country—but there is wide difference of opinion as to the means by which the goal is to be attained. Furthermore those who are "agitating" for a radical reform in medical practice wish to see results obtained speedily. Those who prefer an evolution rather than a revolution of medical practice, and I count myself among this number, are willing to wait longer for results and believe that the final pattern will be better and rest on a more stable foundation. Rapid change may easily destroy the good features of the present system and lower the quality of medical service.

The great bone of contention in relation to Title II is the insurance principle, whether it shall be voluntary or compulsory. Must everyone be insured or may everyone be given the opportunity to be insured, so far as possible through his own resources but with government assistance when it cannot be met by the individual himself? It is estimated that over 90 per cent of the population would be included under the provision of Title II. One can see how profoundly this would influence medical practice. It would precipitate a system of medical practice on a national scale when experience is lacking as to most of the details involved in its operation. We are not prepared in organization, personnel, or facilities for such a universal application of health insurance. There are many voluntary systems of health insurance which have coverage for certain aspects of medical care but only a few which provide complete coverage. We are certainly quite ignorant as to the costs of the plan as proposed in this legislation but no one has suggested that it will not be very large. I believe that the medical profession should oppose Title II of S. 1606 as it is now written.

The extension of voluntary systems of health insurance with government subsidies for the lower income groups would accomplish everything which this bill serves to accomplish and would have many advantages. It would bring about real changes in medical practice but by a gradual modification of existing methods, not a sudden disruption of a system which, after all, is probably producing better results in national health than have been obtained elsewhere by other methods, some of them in line with the proposals of S. 1606. The gradual development of new features would allow for the simultaneous provision of adequate personnel and facilities to operate the expanded services. The utilization of existing voluntary prepayment groups as the basis for a wider inclusion both of individuals and of coverage would preserve the quality of service rendered and the independence of the persons who are able from their own resources to finance their medical care. It would foster local initiative and minimize governmental control, particularly Federal bureaucracy. It would assure a maximum of professional participation and would, I believe, win the support of the medical profession. It would reduce the cost to the government by a very large sum. Whether at this time the tide can be stemmed is a matter of grave doubt. Unfortunately organized medicine has been slow to appreciate the need for an aggressive attack upon the problems of medical care. It has been too often content with a reiteration of the relatively good medical care in this country as compared with other countries and attributed this to our present system of medical care. It has failed to realize that because a thing is good or even the best in the world that it may not be satisfactory. Fifteen years ago the Committee on the Cost of Medical Care in the majority report recommended certain changes which it believed should be made in the provision of medical care in this country which in the main indicated the lines along which developments have taken place—extension of group practice around hospitals and voluntary prepayment plans. Organized medicine gave lip service to some of the features of this report and openly rejected other features. It has belatedly trailed along in supporting the changes as they have occurred. An opportunity for leadership was lost and one wonders whether it can be regained. Small groups within the profession have from time to time urged a forward looking attitude upon their associates but have met more often with scorn and ridicule than with thoughtful consideration of the ideas put forward. It has been difficult for the minority to present their point of view without provoking an emotional response which made impossible an intelligent discussion and weighing of the evidence.

We are now in a difficult situation. The initiative has been taken out of our hands. Proposals have been made and legislation proposed which, to most physicians, seem unwise and quite likely to result in a lowering of the quality of medical care and involving a tremendous financial tax burden. Is it too late to move forward along lines which give real promise of accomplishing the ends which all desire, better medical care for the American people, or must we accept complete governmental control of medical practice? I do not know but that I am convinced something more must be done, and rapidly, than the cautious pronouncement of projected plans. If energetic action could be taken by organized medicine at once to extend voluntary systems of prepayment for medical care, if real support could be given to the principle of group practice, if efforts could be made to strengthen co-ordinated hospital service and sympathetic tangible support given to public health officials, we might win back popular confidence and lead the way to a better plan than that proposed in S. 1606 Title II. Without such vigorous leadership by the medical profession I see no hope but to gird our loins and work hard under governmental control to safeguard the high traditions of medical care.

RICHARD M. SMITH, M.D.

April 30, 1946

A CRITICISM OF THE ARTICLE BY PROFESSOR LICHTENSTEIN ENTITLED "THE SYSTEM  
OF MEDICAL CARE IN CHILDREN IN SWEDEN"  
(JOURNAL OF PEDIATRICS, MAY, 1946)

Dear Dr. Park:

I am enclosing herewith copy for the July issue of the JOURNAL OF PEDIATRICS. I hope that what I have written is the sort of critique you want. If not, I should be very glad to alter it according to your suggestions.

You express in your letter of March 29, disappointment that more discussion regarding systems of medical care is not provoked by a column such as is now running in the JOURNAL. Doctors on the whole think in terms of personal problems and individual patients. One gets the definite feeling that they as well as individual laymen have never really thought through to a real comprehension of what any particular system of medical care would mean for them. Wealthy laymen talk as though a system of compulsory insurance would mean free clinics for them and doctors seem to have a very sketchy idea as to how they would probably lead their lives in the immediate and further future should the Murray-Wagner-Dingell Bill pass. This is an obvious and yet a difficult subject to present but I wonder sometimes if it would not be worth while to attempt.

Thank you for the privilege of putting thoughts on paper.

Very sincerely yours,

LENDON SNEDEKER, M.D.

Boston, Mass.

In discussing the article of Professor Lichtenstein it would seem helpful to summarize the salient points of the Swedish system as described by him. These are:

1. *State control of Medical Education.*

Education of doctors is completely the charge of the State and is free to all qualified students. This would be at least equivalent to putting all medical education on a State University basis.

2. *State Regulation of all health services by a National Medical and Health Board.*

3. *Voluntary Health Insurance*, available to all the population and now participated in by more than 41.5 per cent of the population over 15 years of age. Insurance schemes in Sweden may be State controlled, partly subsidized by the State or largely independent. Costs of hospitalization are considerably reduced by State subsidy. Insurance includes "sick pay" or the equivalent of disability insurance. The sick fund reimburses the patient. The doctor is left free to charge his own fees and the patient has a free choice of doctor.

4. *State regulation of hospitals and clinics* by the national Medical and Health Board. Local medical facilities are built and operated by the local authorities with the exception of State institutions for the mentally ill.

5. *State control of Pharmacies.*

Pharmacists are government concessionaires and the prices of pharmaceuticals are fixed by the State.

6. *State control of some of the maternal and child health services.*

For Sweden, this system sounds like a satisfactory compromise between State control and individual initiative. Such a system is possible in a country where the general level of education and social consciousness is high and where the people have faith in the ability and integrity of their government to such a degree that they will submit to considerable regulation. These conditions are not encountered to a similar degree in the United States. Our people are much more impatient of discipline and regulation. Our situation is further complicated by the fact that we are many states with varied population, geography, income, and social standards.

One great objection to the Swedish system is the elimination of the participation by voluntary agencies in education and to a large extent also in hospital and social agency administration. It is our feeling that as long as private philanthropy is able to maintain these voluntary agencies they should be kept as a part of our system. This assures freer



social experimentation. There should, however, be increased opportunities for training in the medical field and government subsidy should be used when and where necessary.

No widespread improvement in health services is possible in this country without some means for more equitably distributing the costs of medical care. The needed funds must come from insurance or taxation. It is our personal feeling that every effort should be made to test out a variety of voluntary medical insurance schemes in this country. These could be independent or state sponsored, but there should ultimately be some means of protecting the interests of the insured person when he moves from one state to another. Doctors should be free to set their own fees, but the system should be sufficiently flexible to permit using other means of remuneration.

Recent experience with compulsory insurance schemes in Italy and with the creaky workings of its old and bureaucratic government, have considerably heightened our apprehensions about the present wisdom of any compulsory national insurance plan. Neither do we think that the present administration of federally controlled health services in this country has shown sufficient flexibility in meeting local problems or in giving the states means of redress against arbitrary administration.

The type of central control and guidance epitomized by the Swedish Medical and Health Board could be emulated to advantage in the United States. Here the first step should be the creation of a Federal Department of Health and a Secretary of Health responsible for the administration of all Federal health agencies.

Our present hospital system needs gradual systematization so as eventually to produce a properly distributed network of institutions adequately equipped and staffed and bound together by ties of mutual respect and cooperation. We have in mind the voluntary plans now operating in Maine and being simulated in other parts of the country. It is obvious that government support and initiative would be necessary in certain parts of the country, but Federal *fiat* cannot take the place of the results produced by local pride and interest.

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Dear Dr. Park:

I have studied with much interest the galley proof which you sent me of the System of Medical Care in Sweden. I have understood that medical care was well regulated in Sweden and this article supports such an understanding. Apparently membership in "sick relief funds" is not compulsory but is enjoyed by about one-half the population of the country, and is subsidized by the State.

It also appears that the road to becoming a qualified pediatrician in Sweden is long but made easier by complete state financial support. The author of the article states that for the moment there are "only about 120" qualified pediatricians in Sweden, but on a comparative total population basis this would be equivalent to about 2,500 pediatricians in the United States, where there are only about 1,700 Fellows of the American Academy of Pediatrics. I don't know how many Diplomates there are of the American Board of Pediatrics. [Over 2,600. Editor.]

I am particularly interested in the doctor's final conclusion. With him, I *believe* that "the duty of the state is, however, to organize medical care in such a manner that every person, irrespective of his income, can procure the best preventive and curative medical care." I note he says "can" and not "must."

I *believe* also that it is well established that "the best preventive and curative medical care" is not as well provided under government control as under the control of organized independent doctors.

I further *believe* that, except where health is a matter of community interest as in the case of possible resulting dependence or in the case of contagion, the freedoms for which we have fought should include the freedom to choose one's medical care, or none. There are many persons who, because of religious or other reasons, do not want any care. And is it also not true that except to save a life a surgeon may not operate on a patient against his will?

These three beliefs are compatible: Doctors should continue to organize and run group health cooperatives and associated hospital services; a community government might well give aid such as to underwrite the premium payments of those in the community who are proven too poor to pay them; local government should also assist in providing enough hospital facilities, with help if necessary from the individual State or the National Government; but the citizen should remain free to choose as he will—no medical care, prepaid medical service, or the “pay as you go” system.

Cordially yours,

PHILIP M. STIMSON, M.D.

New York City

My Dear Doctor Park:

I have read and reread Professor Liechtenstein's résumé of the Medical Care Program of Sweden in an effort to understand it and to offer constructive criticism as you requested. After a month of thought on the subject I am unable to do so in a satisfactory manner. As I review the program I am impressed with the thought that it is an attempt to furnish care for everyone with the result that for Sweden it may be very satisfactory. The reaction of one to this program depends entirely upon the viewpoint of the individual. One who is basically socialistic in his viewpoint would perhaps feel that such a program is ideal. To another, equally interested in the welfare of the entire nation but who is basically an individualist, the program would present numerous serious objections. To me the most serious criticism would be that under such a program a large portion of the medical profession of the United States would find it so unattractive that in the future such men would not be attracted to the practice of medicine and the quality of medical care would deteriorate.

I have not submitted specific criticisms of the program which has some excellent features because I would have to go into detail and I do not have sufficient information as to the program. I should be glad to discuss this matter with you some time when the opportunity presents itself.

Very truly yours,

EDGAR E. MARTNER, M.D.

Detroit, Michigan

Dr. Durand in writing me in regard to a personal matter expressed his admiration for the views of Dr. James Wilson published in the February issue of the JOURNAL (28: 231, 1946) and in substance stated that he thought Wilson had put his finger on the crux of the problem and that the development of medicine ought to be in the lines indicated by Wilson, essentially toward the education of more and better educated doctors. I replied asking Dr. Durand if he would be willing to amplify his views in another letter so that I could publish it in the Column and I raised the question if it were possible to embark on a policy of educating more and better doctors unless at the same time there were created some new outlet which created a need. Dr. Durand very kindly acquiesced and the letter from him which follows is the result.

I might add that I, too, liked exceedingly Dr. Wilson's suggestions and think that such a plan as he advocated may be possible, if the Hill-Burton Bill becomes a reality. If the Hill-Burton Bill is passed, the new requirements might furnish the medical schools with a requisite reason and means for increasing their student body and for raising their standards of education.

Dr. Durand's letter is as follows:

Dear Doctor Park:

E. A. P.

I am enclosing a somewhat expanded expression of my views suggested by Dr. Wilson's letter. You can use it if you think it should be published. I think we all feel as you do, that changes are coming and probably without our having much to say about it. I cannot feel that “free” medical care for the children of America is going to bring anything but a rapid deterioration of the quality of such care.

You asked me if Dr. Wilson's suggestion were not equivalent to doing nothing at all. I would certainly rather let the very great progress which has taken place in Pediatrics and the care of children, which I have observed during my 30 years of practice, continue, than to have the Government take the matter out of our hands and do things that I think would greatly harm both patients and doctors.

Perhaps we will not be able to prevent these measures going through, but at least we should make as good a fight as we can for our principles. I think the average doctor cherishes his personal freedom more than any other man in the country and I am sure that 90 per cent of the Academy members are going to feel that the passage of the Pepper bill deprives them of their freedom.

Carrying out the provisions of the bill will mean putting the work in the hands of men as incompetent as those who are now caring for the veterans under the Veterans' Bureau.

I believe the majority of Pediatricians who are now established in practice will refuse to cooperate.

Sincerely yours,  
JAY I. DURAND, M.D.

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Dr. Wilson's contribution to the Social Aspects of Medicine Department of the February, 1946, JOURNAL OF PEDIATRICS seems to me a very important pronouncement which should be considered by all Academy members and those seeking governmental control of the medical care of children.

It seems to me a self-evident fact that better care for more of our children cannot be provided until we have more well-trained doctors. No amount of tax money spent for "free" care can accomplish this. Rather, it will greatly lower the quality of medical care for two reasons:

*First.*—There will not be the incentive for men to seek more and more graduate instruction when they are government employees.

*Second.*—The doctors' offices will be so crowded with children having little or nothing wrong with them that particular attention to the more serious cases will be impossible.

In regard to the governmental care of the sick, pediatricians returning from England tell me that American parents would not wait as patiently nor be satisfied with the brief examinations and explanations of the findings as the English, who seem quite long suffering.

The panel physicians have not had special pediatric training nor is the system conducive to the improvement which comes from personal interest in the individual case and the intensive study of the case and the pertinent literature. In consequence, many children are sent to London for consultation often from considerable distances.

Some of the London pediatricians are quite the equal of any in the world but they are relatively few well-trained men and consequently they can devote little time to each patient.

After coming long distances and, in some instances, waiting several hours, the parents are told very little except that the consultant is sending the information back to the doctor who referred them.

In my experience, I have rarely found such consultations satisfactory to the consultant or very beneficial to the patient.

Comparatively small amounts of tax money spent for educating young doctors, providing them with enough money to live on and even supporting a wife during a two- or three-year period, would raise the quality and increase the quantity of good medical care for children. These men, filling residencies in good hospitals, working under direction in out-patient clinics, would raise the standard generally and provide teachers for those who would follow in their footsteps.

This plan, of course, would not have the political appeal that giving "free" medical care would have and probably will not be seriously considered by politicians, but I do feel that something of this kind must be done if the real progress which we have made during the past forty years is to be accelerated.

JAY I. DURAND, M.D.

The following letter is to correct a misstatement which appeared in the Column in January.

May 10, 1946

Dr. F. F. Tisdall,  
Toronto, Ontario

My dear Fred:

It was very kind of you to send me a copy of "Social Aspects of Medicine," which I have read with interest.

By the way, in the letter of Dr. J. Harold Root of 103 North Main Street, Waterbury 14, Conn., the following statement appears: "There is a panel system in England, Australia, New Zealand, Canada, and most of the other government managed plans."

You might like to point out to Dr. Park that this statement of course is incorrect insofar as Canada is concerned—there is no panel in Canada as there is no health insurance in Canada.

With kind regards, I am,

Yours sincerely,

T. C. ROUTLEY,  
General Secretary, Canadian Medical Association

# News and Notes

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The *Annual Meeting of the Academy* will be held at the William Penn Hotel, Pittsburgh, Pa., November 13 to 16, 1946. All hotel reservations will be made through the local convention bureau, and application blanks for hotel rooms will be mailed later to each Fellow.

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| WANTED—Back volumes of THE JOURNAL OF PEDI-  
| ATRICS for European medical schools and pediatric clinics. |

Requests are being received from England, Holland, Belgium, Sweden, and other European countries for back volumes of THE JOURNAL OF PEDIATRICS either to replace sets lost as the result of enemy action or to complete sets by filling in the volumes which were prevented by the war from entering the countries. Two complete sets have been requested, one of which has already been donated. In addition, for example, there is one request for Vol. 15 (1939) through Vol. 27 (1943), and another for Vol. 19 (1941) through Vol. 27 (1945).

The following single numbers will complete volumes now in the hands of the Editors and make them available for shipping:

Vol. 17 (1941) No. 1, January

Vol. 25 (1944) No. 1, July

Vol. 24 (1944) No. 1, January

Vol. 26 (1945) No. 3, March

With these missing issues plus Vols. 18 (1941), 19 and 20 (1942), 21 and 22 (1942), and 23 (1944) another request can be filled.

Doubtless many more requests will be received and the Editors urge that anyone having a set or the volumes desired who is willing to donate them to the European libraries or clinics will communicate with Dr. Borden Veeder, 3720 Washington Avenue, St. Louis, who will maintain a file of available Journals.

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The following promotions of Fellows in Service have been reported to the JOURNAL:

Major Seymour Fisher, Springfield, Ill., to Lieutenant Colonel

Major Daniel J. Pachman, Chicago, Ill., to Lieutenant Colonel

The following Fellows have been released from Service:

Dr. Harry S. Andrews, Louisville, Ky.

Dr. J. Lewis Blanton, Clifton Springs, N. Y.

Dr. Jack Chesney, Knoxville, Tenn.

Dr. Clan L. Douglas, Detroit, Mich.

Dr. A. Alvin Fisher, Canton, Ohio

Dr. Alexander N. Freed, Cleveland, Ohio

Dr. Frederick B. Joy, Seattle, Wash.

Dr. Edmund N. Joyner, III, New York, N. Y.

Dr. Albert P. Knight, Waverly, N. Y.

Dr. Dennis D. Kovan, Detroit, Mich.

Dr. John T. Leshe, Decatur, Ga.

Dr. Matthew M. Lewison, Chicago, Ill.

Dr. Abe Matheson, Chicago, Ill.

Dr. Carl J. Ochs, Cincinnati, Ohio

Dr. D. William Scott, New York, N. Y.

Dr. Donald C. Shelby, Beverly Hills, Calif.

Dr. Harry B. Silver, Culver City, Calif.

Dr. Brick P. Storts, Jr., Tucson, Ariz.

Dr. H. Beril Warshall, Brooklyn, N. Y.

Dr. Daniel A. Wilcox, Mt. Kisco, N. Y.

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The death of Dr. Joseph C. G. Regan, Brooklyn, N. Y., has been reported to the JOURNAL.

# The Journal of Pediatrics

VOL. 29

AUGUST, 1946

No. 2

## Original Communications

### MUMPS: TECHNIQUES OF LABORATORY DIAGNOSIS, TESTS FOR SUSCEPTIBILITY, AND EXPERIMENTS ON SPECIFIC PROPHYLAXIS

JOHN F. ENDERS, M.D.  
BOSTON, MASS.

THE characteristic parotitis and orchitis of mumps have been known to physicians for two thousand years. Meningoencephalitis, pancreatitis, ovaritis, as well as auditory and ocular disturbances—the other most important manifestations of this viral infection—much later received recognition. Together with orchitis these so-called complications not only represent the more serious features, but would also seem to provide the diagnostician, the student of viruses, and the immunologist with problems of great interest.

In view of the well-established background of clinical knowledge, it is rather surprising that investigators have largely neglected this ancient disease—a disease which, because of its ubiquity and comparative benignity, may be regarded as an exceptionally favorable object for experimental study, both in the laboratory animal and in man. Indeed it is only twelve years ago that Johnson and Goodpasture<sup>1</sup> conclusively demonstrated the nature of the etiologic agent. These workers produced typical parotitis in Rhesus monkeys by inoculating them with saliva from patients. In this way the essential tool for further study of the virus was made available. The susceptibility of this monkey has been substantiated by groups of investigators in this country, in England, and in Australia<sup>2, 3, 4</sup>. Until very recently, however, no other species except man and the monkey had been found to be susceptible. This fact somewhat retarded progress in the systematic and detailed study of the factors in immunity although a good deal was learned from experiments which have been carried out in these two hosts. About a year ago, however, Habel<sup>5</sup> succeeded, as did we,<sup>6</sup> in propagating the virus in the developing hen's egg. In our laboratory, thus far, one strain of virus has been carried through thirty-seven serial passages in this medium; and it is now apparent that we are in possession of a simple, convenient, and inexpensive method for producing unlimited quantities of infected material. This discovery has already led to a rapid accumulation of new information concerning the properties of the virus.

Presented before the Meeting of Region I, American Academy of Pediatrics, New York, N. Y., April 2-4, 1946.

Three developments have arisen from investigations made possible by these basic techniques which offer some promise of being of assistance to the practicing physician. The first is the application of the complement fixation test to the diagnosis of mumps infections and to the differential diagnosis of the clinical syndrome of aseptic, or as it is sometimes called lymphocytic, meningo-encephalitis.<sup>7, 8</sup> The second development includes experiments on the significance of the allergic response which follows the intradermal inoculation of small quantities of heat-inactivated virus into the skin.<sup>9, 10</sup> The third concerns the results of studies not yet completed which have been directed toward the development or evaluation of certain specific prophylactic agents.<sup>10, 11</sup>

The technique of complement fixation has been used more and more frequently during the last ten to fifteen years in the diagnosis of viral infections. Therefore, when we were able to confirm the observation that the monkey could be easily infected with mumps virus, it seemed probable that following the subsidence of the acute symptoms, complement fixing antibody might appear in the circulating blood. The extensive involvement of the parotid gland likewise suggested that this tissue might contain sufficient quantities of virus to provide an antigen which could be employed in complement fixation tests. These ideas were tested experimentally and they were immediately verified. It was shown that the sera of normal monkeys or specimens taken during the acute phase of the disease do not fix complement in the presence of a suspension of the infected parotid gland. In contrast, the serum taken from three to five days after the swelling subsides strongly fixes complement. As an example of these immunologic events, the results of successive tests in one animal are presented in Table I. Examination of specimens of acute and convalescent sera from 130 cases of typical epidemic parotitis in man has made it clear that specific complement fixing antibody emerges regularly during convalescence. This fact is illustrated in Table II where the results of tests on pairs of acute and convalescent sera obtained from 8 cases of parotitis are summarized. We have so far encountered no individual in whom the clinical diagnosis was unequivocal who has not responded in this manner. Accordingly we may conclude that when the appearance of antibody or its increase in concentration can be demonstrated, infection with the virus has recently occurred.

As with other serologic methods, the results of this test in mumps can only be regarded as conclusive when two specimens of serum taken at suitable

TABLE I. DEVELOPMENT OF COMPLEMENT FIXING ANTIBODY IN THE MONKEY. INOCULATED 12/31/45

DATE BLED	COMPLEMENT FIXATION TITER
12/31/45	0
1/3/46	0
1/5/46	0
1/8/46	0
1/10/46	0
1/12/46	1:384
1/14/46	1:768
2/5/46	1:384

TABLE II. COMPLEMENT FIXATION—MUMPS PAROTITIS

PATIENT	FIRST BLEEDING (DAYS AFTER ONSET)	TITER (ACUTE PHASE)	SECOND BLEEDING (DAYS AFTER ONSET)	TITER (CONVALESCENT PHASE)
F. C.	0	0	17	1:192
C. D.	1	0	14	1:384
W. G.	0	0	19	1:384
B. N.	1	0	12	1:96
B. T.	0	0	7	1:384
L. W.	5	1:96	12	1:768
S. K.	1	0	4	1:96
M. O.	2	1:32	10	1:1,024

intervals are examined. The first specimen must be secured as soon as possible since it has been found that antibody may appear very rapidly after the appearance of symptoms. In many individuals the test becomes positive within five to seven days after the onset and in some cases even as early as the first or second day. By the fourteenth day nearly all convalescent sera which we have examined have shown high titers of antibody. Rarely a patient did not develop antibody until twenty-one days had elapsed. Therefore, if only two specimens are to be tested, the second should be taken at the end of the third week. But from these findings it is apparent that the serologic diagnosis can frequently be made within a week or less after symptoms have appeared and, in nearly all instances, after an interval of two weeks.

The antibody concentration usually begins to fall after six weeks to two months, although in isolated instances it may persist at an elevated level for longer periods. By the end of six months or a year, however, in nearly all cases, the antibody either has disappeared or has dropped to the relatively low levels characteristic of many persons who have given a history of an attack at some time in the more or less remote past.

Although most of the results which are outlined have been obtained with monkey antigen, the development of the egg technique now furnishes a source of abundant complement fixing antigen which may be obtained at low cost in any well-equipped laboratory.

The behavior of this antibody has been described in some detail because the facts which have been established in unmistakable cases of mumps are of importance when the test is applied to the diagnosis of infections in which salivary gland involvement may be absent or so slight as to leave the observer in doubt. The syndrome of aseptic meningoencephalitis is an illustration of this type of infection. It is now well known that this condition has a varied etiology. In many instances the nature of the agent still remains obscure, but in others a variety of viruses have been incriminated. Identification of the specific virus cannot be made without recourse to laboratory aids, since all these agents may give rise, at least in the earlier stages, to symptoms which are similar and to cellular and chemical reactions in the spinal fluid which are essentially alike. Of the latter, the increase in lymphocytes is, of course, the most salient characteristic. Our findings, as well as the results of studies carried out at the Army Medical School by Plotz,<sup>12</sup> indicate that



among these viruses, that of mumps is very commonly involved. When there is an associated enlargement of the salivary glands or a clear-cut history of exposure to mumps, the presumptive differential diagnosis is not usually difficult. But when these data are absent, the observer may be left in doubt. Meningoencephalitis due to the virus of mumps but without involvement of the salivary glands or even a history of exposure is not infrequent.

By means of the fixation technique we have thus far tested sera and, in a few instances, the spinal fluids from more than one hundred cases of meningoencephalitis. In only 88 of them, however, were the materials taken at an appropriate time. Even among these 88 cases, specimens were often not obtained sufficiently early to enable us to demonstrate an increase of antibody. This was not always due to failure to take the specimen as early as possible, but to the fact that meningoencephalitis may be a late manifestation of infection, appearing after antibody formation has already begun. In consequence a high titer, i.e., 1:192\* or over, may be found at the onset of encephalitis. Yet even when an increase cannot be demonstrated, such high titers under these circumstances may be regarded as *presumptive* evidence of recent infection, since it has been shown by many hundreds of tests in normal individuals that the titer is rarely 1:96 and has only once been found to exceed 1:192.

RESULTS OF MUMPS COMPLEMENT FIXATION TESTS  
IN 88 CASES OF MENINGOENCEPHALITIS

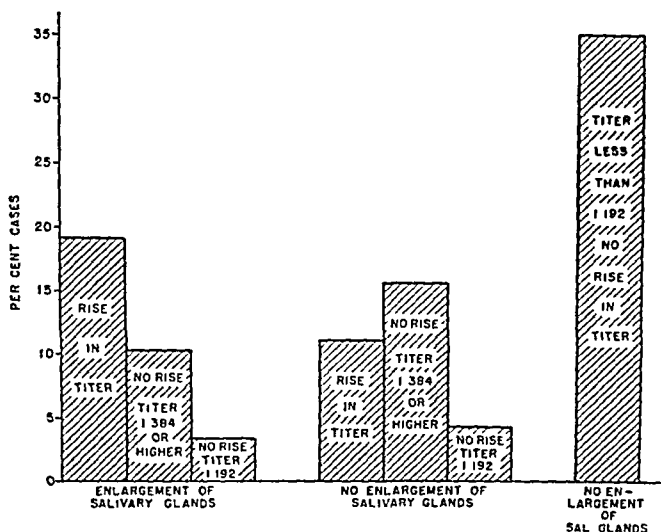


Fig. 1.

With these facts in mind, we may examine the results obtained in the 88 cases which are presented in Fig. 1. It is clear that on the basis of the serologic criteria just mentioned, roughly two thirds of them could be classified

\*With the exception of the data included in Figs. 1, 2, and 3, titers are expressed in terms of the final dilution of serum before the addition of sensitized cells. In the technique which we have employed, this is equivalent to 3 times the initial dilution which is that more often reported. For a more complete discussion of the application of the complement fixation test to the diagnosis of meningoencephalitis, see reference.\*

as presumptively or definitely (increase in antibody demonstrated) associated with a recent infection with the virus of mumps. But of these only about one-half presented signs of salivary gland involvement. This varied from frank parotitis to very questionable enlargement of a submaxillary or a sublingual gland.

When salivary gland involvement was entirely absent, a positive test afforded the only direct indication of the etiology, although in certain instances a clue was also given by a history of recent exposure. Conversely, because of the evidence for the specificity of the antibody response, it would also seem justifiable to conclude that the disease in those who showed neither an increase in antibody nor a high titer was not caused by the virus of mumps.

It is of interest to note that the clinical diagnosis made in these 88 cases included "benign aseptic meningoencephalitis," "mumps meningoencephalitis," poliomyelitis without paralysis, and lymphochoriomeningitis.

Tests for the presence of antibody in the spinal fluid were not usually done, but of 11 specimens which were examined, antibody was detected in only 3. These results show that although antibody may occasionally enter the spinal canal, it does this infrequently and so from a practical standpoint it would appear useless to test for it.

These various points may be emphasized by the findings in two cases due to mumps encephalitis which are presented in Figs. 2 and 3.\* Fig. 2 shows the course of the disease in a 16-year-old boy whose case was diagnosed as typhoid fever on admission to the hospital because of high fever, low white count and slow pulse, and the fact that his spinal fluid was negative on admission. Shortly afterward signs of meningeal irritation were observed and the spinal fluid cell count rose to 270. When the temperature fell and some symptoms cleared, he developed a very slight orchitis and parotitis. The complement fixation test revealed a fourfold rise in antibody which is considered to be diagnostic. In Fig. 3 are summarized the salient features of meningoencephalitis in a 4-year old child in whom no signs of salivary gland enlargement were observed. Again the complement fixation test revealed a fourfold increase in antibody.

The course of lymphochoriomeningitis in a man, 25 years old, as shown in Fig. 4 may be compared with that of this child. It is clear that from the clinical picture the two cases could not have been distinguished with certainty. But the man with lymphochoriomeningitis, from whose spinal fluid the virus was isolated, gave a negative complement fixation test for mumps.

It should be pointed out that this test method can also be employed in the determination of resistance. This application is based on certain considerations: it has been shown that a low concentration of antibody may persist indefinitely in many individuals following an attack of the disease which nearly always confers permanent resistance.<sup>9, 10, 13</sup> Thus a positive test, whenever obtained, may be accepted as evidence of previous infection and hence of im-

\*We are indebted to Dr. Charles A. Janeway for the figures and the clinical notes on these two cases of mumps meningoencephalitis and the case of lymphocytic choriomeningitis subsequently mentioned.

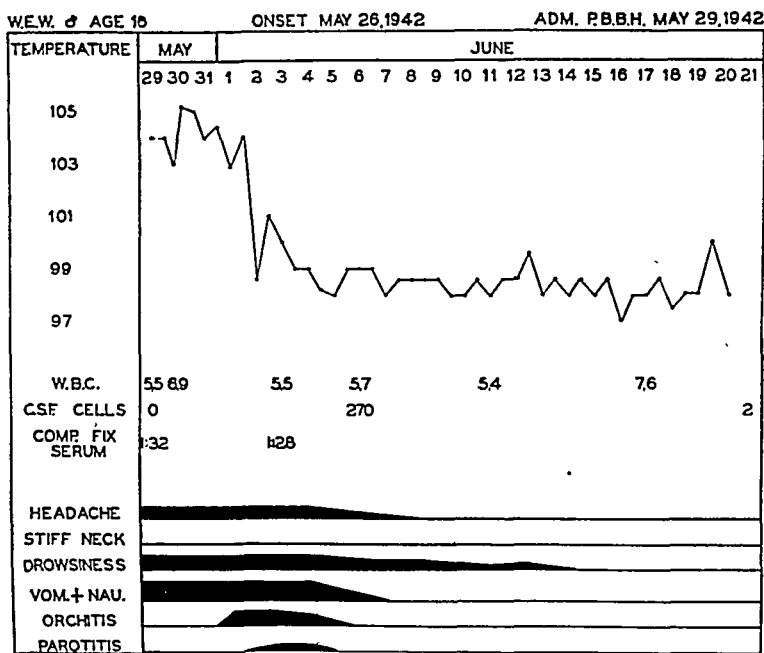


Fig. 2.—Mumps meningoencephalitis with orchitis and slight parotitis.

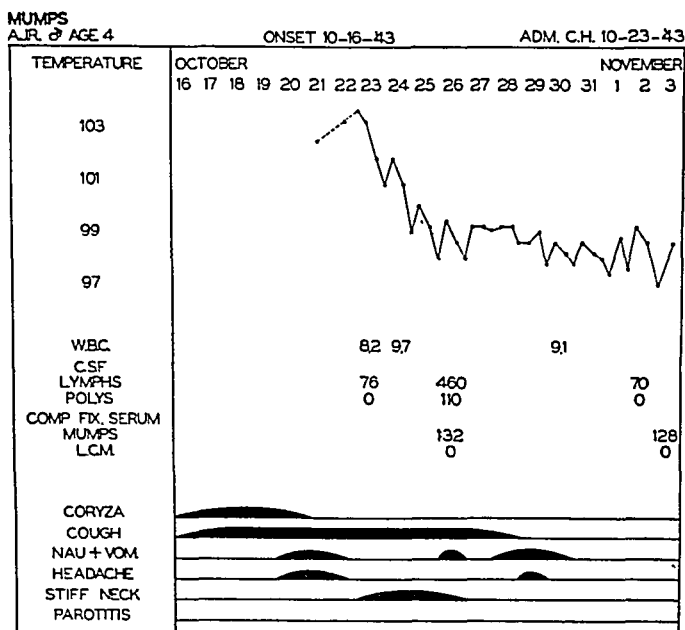


Fig. 3.—Mumps meningoencephalitis without other manifestations of infection.

munity. That such infection may not always be characterized by parotitis or some other overt manifestation but may be subclinical has also been demonstrated. The experimental data supporting this latter statement are not presented here, but they leave no doubt that inapparent infections—long suspected on epidemiologic grounds—are frequent.

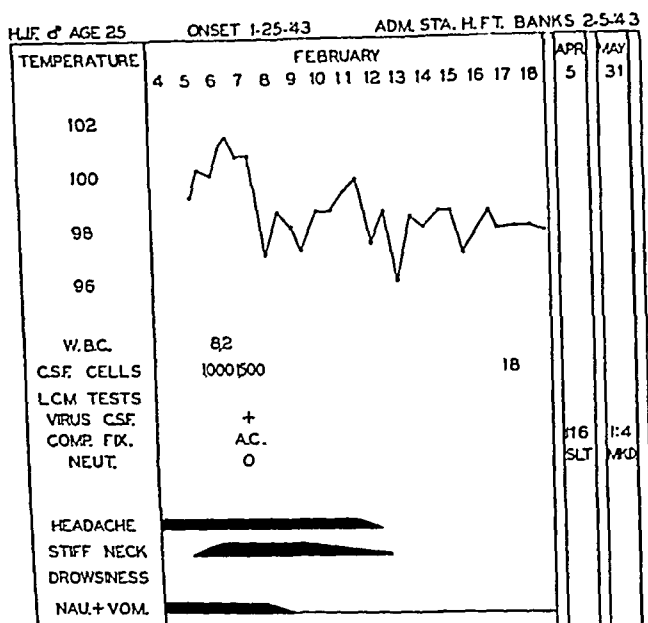


Fig. 4.—Lymphocytic choriomeningitis.

The occurrence of subclinical attacks as well as the well recognized unreliability of a history of mumps as given by the average person make clear the need of some sort of a test for susceptibility and resistance—a need which would immediately become a necessity should effective procedures for vaccination or serum prophylaxis be devised. But in this role the complement fixation test presents certain disadvantages because of the complexity of the technique and the fact that, in a not inconsiderable proportion of persons, following infection the antibody falls below the detectable level. Therefore another method was sought. It has been known for many years that the immediate reaction following vaccination against smallpox in immune individuals is an allergic response which may even be produced with heat-inactivated virus. It seemed possible that the individual immune to mumps might show a similar behavior. We therefore inoculated by the intradermal route a few persons who were able to give unequivocal histories of mumps with 0.1 c.c. of a dilute saline suspension of infected monkey parotid inactivated by heating at 65° C. for 20 minutes. Local inflammatory reactions characterized by erythema and slight induration ranging from somewhat over 10 to 30 or 40 mm. in diameter were observed after 24 and 48 hours. Such reactions did not ensue following

the inoculation of normal monkey protein nor were they observed in about one-half the people without history of mumps who were likewise tested at that time. Moreover it was shown that persons who failed to respond before or immediately after the onset reacted strongly following convalescence.<sup>7</sup> These preliminary observations, which in general have been substantiated by a large number of subsequent studies,<sup>14</sup> indicated that the person previously infected, whether overtly or subclinically, becomes, in nearly all instances, hypersensitive to the virus. This hypersensitivity apparently may persist for many years and is often present in those whose complement fixing antibody can no longer be demonstrated.

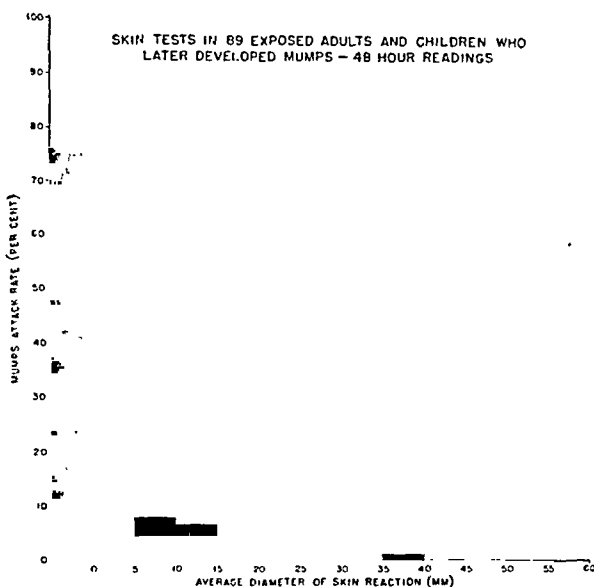


Fig. 5.

The procedure of skin testing thus seemed to offer a simple and convenient method of determining susceptibility or resistance; and so, in collaboration with Stokes and Maris, a considerable amount of effort has been expended to obtain a satisfactory quantitative estimate of its accuracy and to establish more securely its significance in relation to the immunologic status of the individual. With these objectives in mind, a number of groups of children and adults were tested shortly before or soon after they were exposed to mumps. Most of them were living in dormitories of schools and institutions where the intimacy of contact tended to insure intense exposure. A total of 89 cases of mumps developed among these groups after skin tests had been carried out. As shown in Fig. 5, nearly 80 per cent of these cases occurred in those who gave no reaction whatsoever. The others appeared in individuals who responded in some degree to the inactivated virus. Over one-half of these reactions, however, were less than 11 mm. in diameter. Thus more than 90 per cent of the cases developed in persons who failed to react at all or whose reactions were

minimal. A few cases appeared in those whose reactions were larger, but in most instances not exceeding 11 to 15 mm. in diameter. Taking reactions less than 11 mm. in diameter as negative, i.e., as signifying presumptive susceptibility, it would seem possible by means of the skin test to distinguish the susceptible from the nonsusceptible individual within an error of 10 per cent or less.

The relations between skin-reaction size and susceptibility or resistance are given additional emphasis in Fig. 6 where the attack rates of mumps are plotted against the distribution of reaction-sizes. It will be seen that about one-third of the negative reactors developed mumps following exposure. Those with reactions less than 11 mm. showed about one-half this attack rate. In contrast the attack rate for those with reactions ranging from 11 to 15 mm. was only about 7 per cent, and it was still less among the group with reactions greater than 15 mm. It may be concluded, then, that the skin test affords a reasonably accurate index of immunity or susceptibility. It is clear, however, that as with all such procedures, there is inherent in the method a certain degree of error which diminishes rapidly as the reaction-size increases.

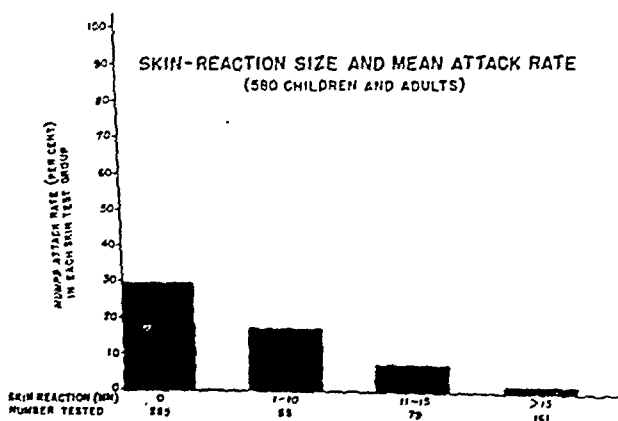


Fig. 6.

Additional interesting evidence for the correlation of resistance with a positive skin test is revealed by a comparison of the attack rates with the incidence of positive tests in various closed communities and in families where small epidemics have been studied. From Fig. 7 it will be seen that when the proportion of positive tests in a group was 50 per cent or less, the attack rate in all but one epidemic ranged from 40 per cent to about 10 per cent. On the other hand, when the incidence of positive tests exceeded 50 per cent, the attack rates were all under 5 per cent. This inverse relationship between attack rate and positive test might have been predicted from generally recognized epidemiologic principles if the test were indeed an index of immunity. Should further trials confirm these data, it is evident that the test could be employed in exposed groups as a means of obtaining a rough idea as to whether a large or small number of cases might subsequently be expected to develop.

The skin test studies just described have all been done with preparations of infected monkey gland. A limited number of observations, both Habel's<sup>5</sup> and our own,<sup>14</sup> have shown that materials from the infected egg can also be employed as a skin test agent.

Certain investigations which have been carried out during the last three years to determine the prophylactic value of materials of human origin containing mumps antibody. As early as 1942, it was demonstrated<sup>15</sup> in our laboratory that in the gamma globulin prepared by Cohn and his associates from large pools of normal plasma the mumps complement fixing antibody was concentrated from 15 to 25 times. With this fact in mind, Stokes and Maris administered 8 c.c. of globulin to each of 25 institutionalized children who were members of a group of 66 which had been exposed to mumps and whose com-

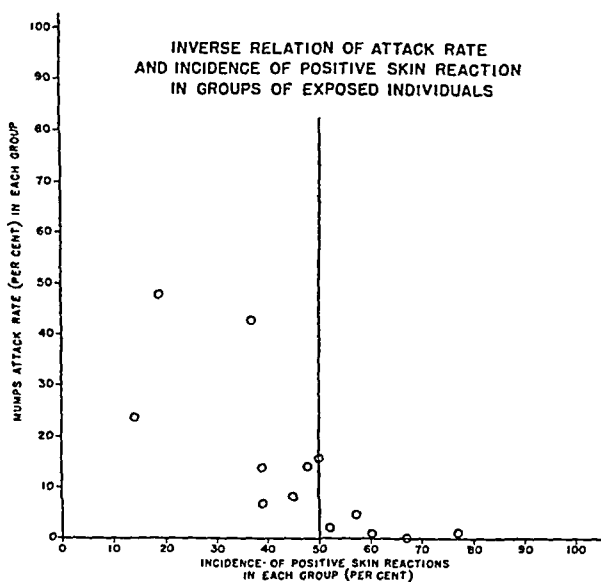


Fig. 7.

plement fixation tests were at this time negative. From the sixth to the sixteenth day after the globulin was given, 10 cases of the disease appeared among those who had received it and 16 cases among the 41 individuals who were not injected.<sup>16</sup> This clear-cut negative result shows that the normal human gamma globulin, which has proved effective in the prevention of measles, is of no value in the prophylaxis of mumps. From observations made on 154 patients with early mumps, of whom 67 received the globulin, Gellis, McGuinness, and Peters<sup>17</sup> concluded that this material did not prevent the development of orchitis even when administered in doses as large as 50 c.c. and before any signs of testicular involvement were present. Calculated on the basis of the antibody concentration, this dose of globulin would be equivalent to about 1,250 c.c. of normal human plasma.

TABLE III. ORCHITIS IN MUMPS PATIENTS INOCULATED WITH GAMMA GLOBULIN CONCENTRATE OF MUMPS CONVALESCENT SERUM\*

GROUP	NO.	CASES OF ORCHITIS	
		NO.	%
Inoculated with globulin	51	4	7.8
Uninoculated	51	14	27.4

\*After Gellis, McGuinness, and Peters.<sup>17</sup>

On the other hand, these same authors obtained results which indicated a prophylactic effect following the administration of 20 c.c. of a gamma globulin concentrate prepared from a large pool of convalescent mumps sera. A summary of their findings is given in Table III. There was in this material 20 times as much complement fixing antibody as in the convalescent plasma and 10 times as much as in the normal gamma globulin. The dose injected, therefore, was equivalent to 400 c.c. of convalescent serum or 200 c.c. of normal gamma globulin. Obviously this represents a much larger quantity of convalescent serum than has been used hitherto in attempts to protect passively against mumps or mumps orchitis. In the form of serum, even if such amounts were readily available, it would be impracticable to administer.

In the light of these observations, it may be concluded that either the protective factor in the blood of those previously infected is relatively ineffective in neutralizing the virus as compared, for example, with the prophylactic agent in measles, or that it is normally present only in very low concentration. Therefore, the conflicting statements and equivocal results to be found in the earlier literature on the prophylactic value of mumps convalescent serum can be now understood.

A certain amount of direct evidence which indicates that the neutralizing factor as distinct from the complement fixing antibody is indeed present only in small quantities has lately been secured by means of titrations carried out in chick embryos.<sup>18</sup> Decreasing amounts of convalescent serum or normal gamma globulin were mixed with 1 to 25 minimal infecting doses of virus and then inoculated into eggs. It was found that the undiluted antibody solutions completely prevented infection of the embryo but when they were diluted more than 8 times, they exerted no protective effect.

At the moment, then, we may assert that a practical method of serum prophylaxis is not available. Furthermore, unless some means of greatly increasing the neutralizing factor is discovered, there would seem to be little likelihood that in the future passive immunization in mumps will prove to be successful.

Certain experiments have had as their objective the development of a practical method of inducing active immunity.<sup>10, 11, 19</sup> Comparatively recent studies on the immunizing properties of a number of viruses after inactivation by formalin or other agents have proved, contrary to the older view, that such material was capable of inducing an effective resistance against experimental and natural infection. As examples, we may mention the formolized egg-vaccine which has been employed in horses and in man as a prophylactic against



equine encephalomyelitis. Similarly the formol-inactivated influenza virus which is now being used in the Army apparently is capable of protecting a majority of those who have received it. Thus, when it was determined that the infected parotid gland contained large amounts of virus-antigen, we at once proceeded to ascertain whether a suspension of this tissue, treated with small amounts of formalin, would immunize monkeys.<sup>3</sup> Two doses of 0.5 c.c. each were administered subcutaneously at an interval of five days and a challenge inoculation of active virus was introduced into the parotid gland on the seventh to the ninth day following the second injection of vaccine. The results showed that approximately two-thirds of 16 vaccinated animals exhibited signs of increased resistance. A further indication of the antigenicity of the vaccine was afforded by the fact that complement fixing antibody developed in about one-half of these vaccinated animals.

On the basis of these findings, Stokes and Maris, with our collaboration, have carried out four experiments in groups of institutionalized children with the consent of their parents or guardians. Presumptively susceptible individuals were selected by means of the complement fixation test in all cases and by means of the skin test in two of the experiments. The skin test was not uniformly applied because of the possibility that this procedure itself might in some instances give rise to increased resistance. Two 1 c.c. doses of formolized virus were given subcutaneously in all the vaccinated groups with a single exception in which three doses were administered. In the first two experiments the immunity was challenged by inoculation of active monkey virus introduced directly into one parotid gland via Stensen's duct. In the last two experiments the active virus was sprayed into the oral cavity. In each experiment were included groups of controls who did not receive the vaccine but were inoculated with active virus.

TABLE IV. VACCINATION OF HUMAN BEINGS WITH FORMOL-INACTIVATED MUMPS VIRUS

EXP.	ROUTE CHALLENGED	VACCINATED		CONTROLS	
		RESISTANT	SUSCEPTIBLE	RESISTANT	SUSCEPTIBLE
I	Stensen's duct	5	1	0	6
II	Stensen's duct	6	2	3	4
III	Oral cavity	11	6	1	8
IV	Oral cavity	9	1	4	6
	Total	31	10	8	24
Vaccinated groups: resistant				76%	
Control groups: resistant				25%	
Difference				51%	
Difference					
Standard error of the difference				4.3	

The results obtained in these four experiments are summarized in Table IV. It will be seen that about three-fourths of the vaccinated children presented evidence of increased resistance as contrasted with about one-fourth of those in the control groups. This difference of about 50 per cent is statistically significant. It will also be noted that the degree of protection which may be attributed to vaccination is of the same order of magnitude as that recorded in the monkey-vaccination experiments. These results are definitely encouraging

but the incidence of protection is not as great as might be wished. Moreover, it is probable that the immunity would be of short duration like that induced by other inactivated viruses such as influenza.

At this point it should also be made clear that the formolized vaccine appears to have no prophylactic effect when given during the incubation period of the natural disease. A study carried out by Stokes and Maris in family groups has not revealed any significant difference in the incidence of mumps among 50 skin test-negative individuals of whom 27 were given the vaccine after exposure.<sup>19</sup> There was an indication, however, that this procedure might have reduced appreciably other more serious manifestations such as orchitis or encephalitis.

As yet trials in human beings with formolized virus obtained from the egg have not been made, although one experiment in monkeys has demonstrated the prophylactic properties of such material. Unlimited quantities of the virus grown in this medium could now be obtained, if required, for the production of vaccine. The egg virus could also be concentrated by means of adsorption and elution from the red blood cells of the chicken in a manner entirely analogous with that now employed by Francis in concentrating the influenza virus for use as a vaccine; since, as we have recently shown,<sup>6</sup> the mumps virus becomes adsorbed on red cells, causes their agglutination, and is again spontaneously released in the same manner as that of the influenza virus.

Cultivation of mumps virus in the egg has, however, suggested another and perhaps more promising line of attack on the problem of active immunization. One might expect that, following continued passage in this host, the pathogenic properties of the virus would be reduced for the monkey and for man. As far as the monkey goes, experiment has already verified this expectation.<sup>20</sup> After 15 egg passages, the virus inoculated into the parotid glands of two monkeys failed to produce swelling in one and produced only moderate swelling in the other. After 25 egg passages the virus caused no swelling in four monkeys which received this material. In both experiments the animals, however, were found to be immune on subsequent challenge with active monkey virus. Studies are now in progress to determine whether this living, attenuated, egg-passage virus will produce immunity in man without giving rise to the typical disease. Some evidence that the pathogenic properties for the human being have been markedly reduced is available, but as yet it has not been determined whether resistance is increased following oral inoculation of such egg-passage material. The establishment of an effective procedure of this sort would, however, seem to be a definite possibility and, should it become available, one might anticipate from the effect of the attenuated vaccines employed against smallpox and yellow fever that the immunity so induced would be highly efficient and permanent.\*

\*The investigations leading to the results which have been reviewed in this paper were carried out as a project of the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

## REFERENCES

1. Johnson, C. D., and Goodpasture, E. W.: *J. Exper. Med.* 59: 1, 1934.
2. Findlay, G. M., and Clarke, L. P.: *Brit. J. Exper. Path.* 15: 309, 1934.
3. Enders, J. F., Kane, L. W., Cohen, S., and Levens, J. H.: *J. Exper. Med.* 81: 93, 1945.
4. Swan, C., and Mawson, J.: *M. J. Australia* 1: 411, 1943.
5. Habel, K.: *Pub. Health Rep.* 60: 201, 1945.
6. Levens, J. H., and Enders, J. F.: *Science* 102: 117, 1945.
7. Enders, J. F., Cohen, S., and Kane, L. W.: *J. Exper. Med.* 81: 119, 1945.
8. Kane, L. W., and Enders, J. F.: *J. Exper. Med.* 81: 137, 1945.
9. Enders, J. F., and Cohen, S.: *Proc. Soc. Exper. Biol. & Med.* 50: 180, 1942.
10. Enders, J. F.: *Tr. & Stud., Coll. Physicians, Philadelphia* 13: 23, 1945.
11. Stokes, J., Jr., Enders, J. F., Maris, E. P., and Kane, L. W.: *Am. J. Dis. Child.* 69: 327, 1945 (Abs.).
12. Plotz, H.: Personal communication.
13. Maris, E. P., Enders, J. F., Stokes, J., Jr., and Kane, L. W.: *J. Exper. Med.*, in press.
14. Enders, J. F., Kane, L. W., Maris, E. P., and Stokes, J., Jr.: *J. Exper. Med.*, in press.
15. Enders, J. F.: *J. Clin. Investigation* 23: 510, 1944.
16. Enders, J. F., and Levens, J. H.: Unpublished data.
17. Gellis, S. S., McGuinness, A. C., and Peters, M.: *Am. J. M. Sc.* 210: 661, 1945.
18. Enders, J. F., and Levens, J. H.: Unpublished data.
19. Stokes, J., Jr., Enders, J. F., Maris, E. P., and Kane, L. W.: *J. Exper. Med.*, in press.
20. Enders, J. F., and Levens, J. H.: *J. Immunol.* In press.

## JUVENILE RHEUMATOID ARTHRITIS

### A STUDY OF FIFTY-SIX CASES WITH A NOTE ON SKELETAL CHANGES

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SINCE the organization of an arthritis clinic at Columbia Presbyterian Medical Center in 1928, we have had the opportunity to observe fifty-six cases of rheumatoid arthritis in children. This group includes those cases in which the onset was at 12 years of age or earlier, and represents 4.9 per cent of all cases of rheumatoid arthritis seen in this clinic. While we do not accept a separation of juvenile from adult rheumatoid arthritis, some such arbitrary division was necessary for this discussion.

We have not used the term Still's disease as there seems to be no justification for this special grouping. Most physicians, today, consider such cases as rheumatoid arthritis, modified clinically by the age of the patient. A similar situation arose in the use of the term Felty's syndrome<sup>1</sup> for cases of adult rheumatoid arthritis associated with leucopenia and enlargement of the spleen and liver. It is now generally recognized that these associated findings are a part of rheumatoid arthritis and not a reason for a separate classification. The term Still's disease came into common usage after 1897, when Still<sup>2</sup> separated juvenile rheumatoid arthritis into two groups, (1) those cases of chronic progressive polyarthritis indistinguishable from that seen in adults, and (2) a group with similar pathologic changes in joints but associated with enlarged spleen and lymph glands, and sometimes adhesive pericarditis. The latter was thought to be a new entity. At the time, Still<sup>2</sup> was not aware that such lymphadenopathy and splenomegaly occur, although less frequently, in adults with rheumatoid arthritis. In this country, the classification was further complicated by a misuse of the term Still's disease as synonymous with rheumatoid arthritis in children, rather than applying it only to those cases associated with splenic and lymph gland enlargement. Also there has been a confusing problem in patients followed for a period of years where the diagnosis of Still's disease was made in childhood. As they became young adults relapses of the disease occurred, and then these patients were considered to have rheumatoid arthritis. For these reasons, we agree with those who have discarded the term Still's disease. One of the most recent classifications of arthritis, that of the New York Rheumatism Association, includes such cases under *Rheumatoid Arthritis, juvenile type*.

In certain cases in this series which were followed for several years the diagnosis was at first uncertain. This was particularly true when it was necessary to differentiate between rheumatoid arthritis and rheumatic fever. A therapeutic trial with salicylate was helpful in some of these cases. The problem was further

From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, Columbia University, College of Physicians and Surgeons. Many of the patients were originally seen in Babies Hospital. We wish to thank Dr. Rustin McIntosh and his staff for permission to report them.

complicated by the fact that seven patients had electrocardiographic changes distinct enough to be labeled myocardial damage or carditis. In such instances as these, time has been our most valuable diagnostic ally. Six patients showed a return of the electrocardiographic pattern to normal on subsequent examinations. A follow-up record was not available in the seventh. Rheumatoid arthritis is a systemic disease even though by definition we emphasize the condition of the joints, and we have learned to expect a variety of systemic lesions, from the adhesive pericarditis described by Still to many other lesions reported in recent years.<sup>3, 4</sup>

Even though the diagnosis be doubtful early in the disease, if periarticular swellings, contractures, loss of motion, joint effusions, characteristic x-ray changes, muscle atrophy, subcutaneous nodules, enlarged lymphatic glands, splenomegaly or hepatomegaly appear, and if these changes, including various types of joint involvement, persist over a period of years, we must say they are cases of rheumatoid arthritis, regardless of associated systemic changes.

One of us (R. H. B.) has described<sup>5</sup> three types of cases where the differential diagnosis between rheumatic fever and rheumatoid arthritis is difficult, viz.:

1. Chronic adult rheumatic fever
2. Rheumatoid arthritis following previous bouts of rheumatic fever
3. Acute onset of rheumatoid arthritis, with subsequent chronic progressive arthritis. Nearly all of the diagnostic problems in this study were in the last category.

In addition to objective clinical studies, x-ray and laboratory tests were done in most cases, including urinalysis, blood count, erythrocyte sedimentation rate, tuberculin skin test, Kline reaction, antistreptolysin-O determination, and agglutination of Group A hemolytic streptococci. Throat cultures and electrocardiograms were obtained when indicated.

*Age and Sex.*—Chart I illustrates the age and sex incidence of juvenile rheumatoid arthritis in our series. The earliest age of onset was 14 months. Still<sup>2</sup> found the ratio of females to males to be only 1.5 to 1. In our series, the ratio was 5 females to 1 male, or approximately the same as in adult rheumatoid arthritis. This finding corresponds with that of the series reported by Colver.<sup>6</sup>

*Family History.*—In 18 instances (32 per cent) a history of possibly related conditions was obtained. These included rheumatic fever, 6; chorea, 1; rheumatoid arthritis, 4; recurrent arthralgia, 2; allergic symptoms (asthma, angioneurotic edema), 3; respiratory diseases, including frequent colds, 4; and "heart disease," 2. In some instances a background of two or more related illnesses was given. This incidence of related illness is much higher than would be found in a similar series of normal individuals.

*History of Preceding or Associated Illness.*—Thirty-two cases, or 57 per cent, had a history of respiratory tract infection including pneumonia, bronchitis, recurrent sore throats, sinusitis, or otitis preceding or associated with the onset of arthritis. Seven cases, or 12.5 per cent, had a preceding or concurrent

history of gastrointestinal disturbance such as poor weight gain, anorexia, diarrhea, or constipation. Thirty-nine cases (69 per cent) had a history of frequent ear, nose, and throat infections at some time in the course of the illness. This seems to bear out the observation of many physicians that the incidence of associated respiratory infections is much higher in these patients than in the general population. Other than the gastrointestinal disturbances mentioned, it is our impression that an unusually large proportion of these patients are characterized by their parents as "colicky," "finicky eaters," nervous, or easily upset. Only one patient in this series had previously had rheumatic fever.

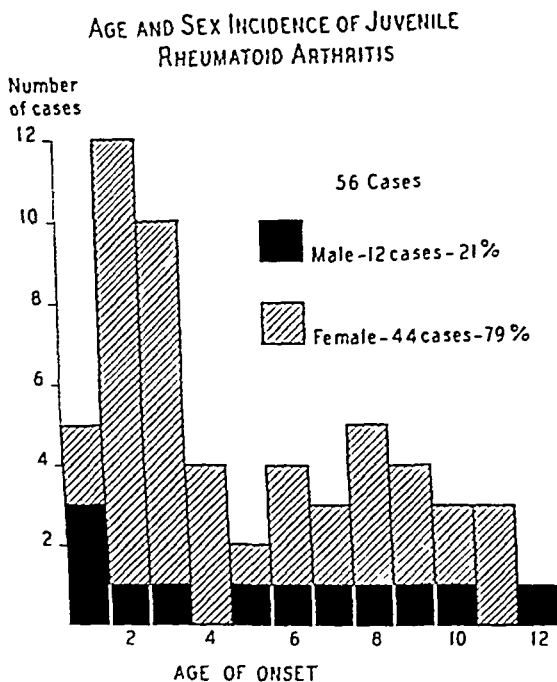


Chart I.

*Physical Findings.*—We have determined the incidence of some of the secondary characteristics commonly associated with juvenile rheumatoid arthritis. There were 13 cases (23 per cent) of hepatomegaly, 17 cases (30 per cent) of splenomegaly, and generalized glandular enlargement of varying degree was noted in 35 cases, or 60 per cent.

In many studies of this form of arthritis, one finds descriptions of flexion deformities of the extremities. This has occurred in our experience usually as a result of improper treatment, particularly the neglect of simple but important measures such as splints and physiotherapy, together with adequate rest.<sup>7</sup> Some patients develop deformities regardless of care given, a number of these can be returned to full physical activity through the intervention of orthopedic surgery when the acute stage has passed.

The reported lack of pain in Still's disease was not characteristic of this series. Practically every patient at some time in the disease has complained

of pain. It has also been stated that the terminal interphalangeal joints are frequently involved in Still's disease as contrasted to the proximal joint involvement in adults. This was seen in some cases but was not of unusual incidence. Subcutaneous nodules were seen in two cases. They were similar in size and distribution to those seen in adult patients with rheumatoid arthritis.

When information was complete enough to draw conclusions, we evaluated the cardiac status. Thirty-one cases (53 per cent) showed no abnormality on physical examination or electrocardiogram; the remaining 47 per cent had some cardiac disturbance. There was a tachycardia in 13 instances, a systolic murmur of varying intensity (never harsh) in 13 cases, and in 7 cases the electrocardiographic variation was great enough to be diagnosed as "evidence of myocardial damage" or "carditis." Six of these reverted to normal in later examinations. A patient whose condition was previously diagnosed rheumatic fever, rather than rheumatoid arthritis, on the basis of electrocardiographic reports, now has an obvious rheumatoid arthritis with typical joint deformities and negative heart on electrocardiographic and physical examination. Still<sup>2</sup> was impressed by the high incidence of adhesive pericarditis in this condition (3 definite and 5 possible instances in a series of 12 cases). It was possible to demonstrate this in one of the two fatal cases in the present series.

*Laboratory Data.*—There was a tendency to moderate anemia in about 80 per cent of the cases, the remainder had essentially normal hemoglobin and red blood cell values. Leucocyte counts showed the most striking deviations from normal. In 37 per cent of the patients, on the basis of the highest count recorded, the leucocyte count was above 15,000, and in 17 per cent of the patients it was above 25,000. In Table I leucocyte counts are compared with prognosis. While correlation is not exact, it is interesting to note that most of the patients showing marked improvement never developed a high degree of leucocytosis, whereas the fatal cases had leucocytosis reaching 30,900 and 36,000, respectively.

TABLE I. CORRELATION OF PROGNOSIS AND LEUCOCYTOSIS (48 CASES)

DEGREE OF IMPROVEMENT	LEUCOCYTE COUNT (IN THOUSANDS)			
	BELOW 15	15 TO 20	20 TO 25	25 OR OVER
Marked	14	1	1	3
Moderate	8	5	0	0
Slight	2	0	0	2
None	6	2	0	4
				(2 deaths)
Total Patients	30	8	1	9

Eosinophile leucocyte counts were done in many cases, particularly if the patients were receiving chrysotherapy. Eosinophilia has been considered in this clinic to be a fairly reliable indicator of early gold toxicity as it was found to precede onset of a rash in adults. Six patients treated with gold exhibited an eosinophile count of 5 per cent or more. Four patients developed this degree of eosinophilia without gold therapy. In two instances the degree of eosinophilia while on chrysotherapy reached particularly high levels. Neither of these patients developed a rash or other toxic symptoms although the eosinophilia fell rapidly when treatment was interrupted. We concluded that eosinophilia may

be an indication of early gold toxicity but its relation to the onset of rash in children is only fortuitous.

Albuminuria of high degree was noted in the patient who developed amyloidosis but in no other instance was it a constant or troublesome feature. One case of persistent albuminuria was hypostatic in nature.

The erythrocyte sedimentation rate was determined by the Westergren<sup>8</sup> method. In most cases, clinical improvement is correlated with the erythrocyte sedimentation rate; however, this is by no means absolute. Many patients with a fairly high erythrocyte sedimentation rate showed moderate or marked improvement, and several patients with a normal erythrocyte sedimentation rate had continued rheumatoid activity. The fall of the sedimentation rate on treatment is not an absolute indication of improvement. The blood Wassermann was negative in all cases tested. Tuberculin skin tests were negative in all but one case. X-ray studies are reviewed in the last part of this paper.

*Bacteriology.*—Of 28 patients tested one or more times, 17 were found to harbor hemolytic streptococci in their throats. Group and type were not recorded but the high incidence of hemolytic organisms seems significant in itself. Bourn and associates,<sup>9</sup> in a study of 1,460 subjects, found throat cultures positive for hemolytic streptococci in 19.8 per cent of children under 9 years of age, in 9.3 per cent of all ages without respiratory infection, and in 11.8 per cent of all ages with respiratory infection.

The antistreptolysin titer<sup>10</sup> was determined one or more times in 24 cases. The median figure obtained, 250, is significantly higher than the upper limits of normal. Other workers have considered any titer above 100 as suggestive of previous hemolytic streptococcus infection.<sup>11, 12</sup>

Streptococcus agglutination tests<sup>13</sup> were done in 35 patients and in only 3 of these was there a positive reaction. One was an adult when the positive reaction was obtained. The experiments of Freund<sup>14</sup> and various others<sup>15</sup> on the relationship of age to immune mechanisms suggested that many of the negative reactions would become positive with increasing age. However, in repeated tests of 17 patients over periods as long as 14 years, no increase in the agglutinating activity of the serum was observed.

*Prognosis.*—Colver<sup>6</sup> has stated that in a series of 37 cases, the duration of disease was never over seven years and he felt that one could predict the cessation of activity within a maximum period. We realize that this is a very difficult thing to evaluate accurately but our experience has not led us to such optimism. One patient in particular, in our series, has had six well-defined periods of activity in a 23-year interval. Twenty-one of 50 cases have had a duration of 5 years or more, and twelve cases have had a duration of 7 years or more. This is in contrast to Colver's series in which there were no cases exceeding seven years' duration.

Removal of foci of infection has had a beneficial effect in isolated cases. In other cases, just as striking results were noticed of an opposite nature with an increase in activity following removal of foci.



Relation of mortality to duration of illness cannot be determined in our series as there have been only two deaths. One of these patients died within a few months of the onset of the disease, the second had had the disease fourteen years. These two fatalities will be reviewed.



Fig. 1.—D. D. (right) at the age of 6 years, 9 months, and before the onset of arthritis. Her sister (left), 1 year, 10 months younger.

*Gold Therapy.*—The results of treatment with gold and with other forms of therapy were studied. Thirty-four patients received supportive measures such as rest, transfusion, splints, physiotherapy, and salicylates. Focal infections were treated and in a few cases vaccines were given. Twenty-two patients received gold as well as the other various measures of treatment. The average course consisted of 600 mg. gold compound,\* but a few patients received 1,000 to 1,200 mg. Others received as little as 95 mg. depending on the clinical picture or signs of toxicity. Because of the small number of cases treated and the extreme variation in total gold dosage, it has been impossible to evaluate comparatively the response to treatment in these two groups.

\*Solganal B Oleosum used in this study was supplied through the courtesy of Schering Corporation, Bloomfield, N. J.

The frequency and severity of toxic reactions produced by gold have been recognized since the introduction of chrysotherapy. Of 22 patients receiving chrysotherapy, 10 had a reaction of mild degree and there were 2 fairly severe reactions. The mild cases included: transient rash, 7 cases; pharyngitis, 2 cases; transient marked eosinophilia (without rash), 2 cases; and transient thrombopenia, 1 case. One patient developed an hepatitis after receiving 95 mg. of gold salt. This case is being reported in detail elsewhere.<sup>16</sup> There was



Fig. 2.—D. D. (right) at the age of 12 years, 7 months, five years and three months after the onset of rheumatoid arthritis. Note undershot jaw and generalized lack of development as compared with normal younger sister (left).

momentary improvement in the arthritis which reverted to its previous level when the jaundice cleared. A second patient developed a rash with nausea and vomiting which subsided with no sequelae after gold was omitted. Of the 7 cases of mild rash we are not at all certain that some of these were not a result of the disease process rather than chrysotherapy, for we occasionally see erythema or vesicle formation in the course of the illness when no specific treat-

ment of any kind is being given. The natural history of Still's disease is often so bizarre that it is easy to blame a medication for some of its manifestations.

*Skeletal Changes.*—Taylor and others<sup>17</sup> have suggested a method of comparing various forms of arthritis roentgenographically. From this work we have used four criteria which seem to be most characteristic of juvenile rheumatoid arthritis: viz., decalcification, bone destruction, joint space narrowing, and soft tissue changes.



Fig. 3—C B X-ray of cervical spine prior to onset of arthritis (Age, 1 year, 4 months)

X-ray studies were available in 47 cases and in all cases studied at least one of the selected criteria was present. In 20 cases, two items were present; in 9 cases, three; and in 7 cases, all four changes were demonstrable. As would be expected, more marked changes were seen in the older patients who had had the disease for a longer time. Joint changes as evidenced roentgenographically are often rather late to appear, just as in adult rheumatoid arthritis.

Taylor and associates concluded that the roentgenologic picture of juvenile rheumatoid arthritis was identical with that of rheumatoid arthritis in adults. For the most part this is true, but in studying a larger series of cases we have noticed additional features peculiar to arthritis in the young age group. Many observers have remarked about the generalized failure of maturity and the bird-like facies in juvenile arthritis since it was first described by Still (Figs. 1 and 2).



Fig. 4.—C. B. X-ray of cervical spine after arthritis had become obvious in fingers and toes. Note fusion of C<sub>2</sub>, C<sub>4</sub>, and C<sub>5</sub>. Patient complained of pain and loss of motion in the neck.

*Cervical Fusion:* Reviewing the x-rays in our series, we discovered instances where a fusion of cervical vertebrae had occurred following arthritis. This change in children has usually been spoken of as congenital failure of segmentation. We feel that this is not a failure of segmentation but a bony fusion resulting directly from arthritis in the involved area. Figs. 3 and 4

show the cervical spine of a child just at the onset of arthritis and twelve years later when the process had become quiescent but pain in the neck persisted.

*Brachydactylia:* Other cases have also exhibited an interesting phenomenon, shortening of fingers or toes which had previously been the site of early involve-



Fig. 5.—R. T. Showing shortening of left middle and right middle and ring fingers. Arthritis severe.

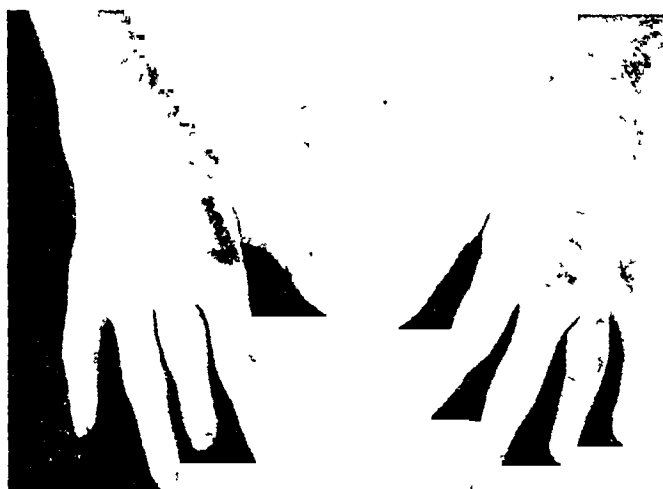


Fig. 6.—C. R. Showing shortening of fingers. Definite rheumatoid arthritis, juvenile type.

ment with arthritis. Some of these patients have early photographs showing the normal fingers before the onset of disease (Figs. 5 and 6.) Similar changes have been described in conditions other than arthritis, such as poliomyelitis.<sup>15</sup> In 56 cases of arthritis, 22 (39 per cent) were discovered to have disturbed

skeletal patterns of varying degree. Fourteen patients (25 per cent had definite brachygnathia, 7 cases (13 per cent) had changes in the cervical spine; one of these was a forward luxation of one vertebra on another; the remaining 6 cases exhibited fusion of two or more cervical segments. Six patients (11 per cent) had shortened fingers or toes (brachydactylia). Fourteen of the cases were aged 3 years or less at onset of their arthritis.



Fig. 7.—C. R. X-ray of hands in Fig. 6.

#### DISCUSSION

The natural history of juvenile rheumatoid arthritis has been discussed on the basis of a study of 56 cases. This is 4.9 per cent of all cases of rheumatoid arthritis seen in this clinic. Still's disease suggests a distinction between conditions the differences in which are not related to the nature of the disease process but to the reaction of the body against that process as it varies in different age groups. Age and sex incidence of arthritis in this juvenile group is about the same as has been reported in other series. Family history and personal history of the patient bear more than an incidental relationship to this condition. The presence of splenomegaly, hepatomegaly, or generalized glandular enlargement is not a necessary part of the diagnosis of juvenile rheumatoid arthritis although it is more frequent than in adult arthritis.

Cardiac changes were seen in some of our patients and, if the arthritis had disappeared early with no residuum, one would be inclined to classify them as rheumatic fever. With persistent arthritic manifestations, however, cardiac involvement seems to indicate the close relationship between the two conditions.

We are no nearer to an elucidation of the etiology of this condition than before, but the high incidence in this series of elevated antistreptolysin titers and throat cultures positive for hemolytic streptococci makes us hesitate to

discard the bacteriologic approach. The many similarities between rheumatic fever and rheumatoid arthritis lead to the interesting conjecture that we may be dealing with the same type of process as has been suggested in the former condition, viz., recurrent hemolytic streptococcal infection and its consequences. In the case of rheumatoid arthritis, one postulates a lag period of months instead of weeks between infection and clinical symptoms, plus a far more insidious onset, as a rule, and an equally insidious remission. These factors make it impossible, using present methods, to incriminate the streptococcus except by inference.

A review of the laboratory data shows an interesting correlation of leucocytosis and prognosis. In 8 patients with leucocytosis over 25,000, only 4 improved, and 2 of the unimproved died. In two cases where eosinophilia became extreme during gold therapy, no rash developed, and in other instances a rash developed without preceding eosinophilia.

A fall in erythrocyte sedimentation rate was correlated roughly with clinical improvement. There were enough exceptions to make minor variations in erythrocyte sedimentation rate alone unacceptable as an index either of activity or of improvement following treatment.

With chrysotherapy we have seen no irreversible toxic results in children and the only fatalities reported in this series were in the nongold-treated group. In our experience, gold therapy is no more dangerous in children than adults. Typical cases in the two groups are reported, including the two fatalities. One of these cases exhibited terminal amyloidosis.

A description of unusual skeletal changes resulting directly from early rheumatoid arthritis is given. These changes usually occur when the disease begins before the second dentition and in the first three years of life.

#### CASE ABSTRACTS

**CASE 12.**—A girl, aged 3 years, complained of swollen right ankle and left thumb for two and one-half months. There was no previous trauma or known infection. At examination, the temperature was 100° F., pulse 140, and the tonsils were enlarged. Patient walked with a decided limp. Laboratory data: Erythrocyte sedimentation rate 32 mm. in one hour; all other values were normal. The patient was discharged in four weeks improved; then arthritis recurred and moved to the left knee. A course of gold salt was given and the tonsils were removed. As a result, her condition was much improved. One year later joint pain and swelling returned. On examination, one observer noted that the patient was developing a receding mandible. A second course of gold therapy was given and joint symptoms subsided.

The child is now 8 years old and is entirely well but for the residual change in the lower jaw (brachygnathia) and slight flexion deformity in three fingers.

Impression: Definite juvenile rheumatoid arthritis with good response to chrysotherapy.

**CASE 20.**—A 3-year-old girl was admitted with fever and generalized glandular enlargement. There was an extensive maternal family history of rheumatic fever and rheumatoid arthritis. Examination revealed a pale, acutely ill child with a discharging right ear, large tonsils, and nasal discharge. No heart murmur was heard but there was tachycardia of 135, generalized glandular enlargement, and polyarthritis. Laboratory data was not remarkable.

Treatment with salicylate and transfusion gave no response; temperature ranged from 100° to 104° F. Tonsillectomy was done in the second week, because of failure of

other measures, with immediate dramatic improvement. Temperature fell, arthritis and adenopathy subsided, and the patient was discharged on the ninth postoperative day.

She was readmitted overnight for a transfusion. In a month temperature again began to rise. Now the liver and spleen were enlarged, pulse was 160 to 180, temperature 103° to 105° F. The urine contained bile, and the stools were acholic. The patient was readmitted in extremis, with skin jaundiced, bleeding gums, and vomiting brown material. Laboratory data: Red blood cells, 3,000,000 to 3,800,000; hemoglobin, 63 to 69 per cent; platelet count, 176,000 to 184,000; white blood cells, 30,900; bleeding time, prolonged. Urine: Albumin 2 plus; red blood cells 1 to 3 per high power field. Blood sugar, 40 mg. per cent, rose to 161. Nonprotein nitrogen, 70.4. Carbon dioxide combining power, 50.4; direct Vandenberg, 4 plus; bilirubin, 4.16. Blood culture: Diphtheroids.

Patient expired on second day after admission.

Pathology report revealed acute yellow atrophy of the liver; jaundice; splenomegaly; subserous, subcutaneous, subendocardial, and myocardial hemorrhage; lobular pneumonia; fibrous pleural adhesions.

Impression: Early polyarthritis with fulminating course, improvement after tonsillectomy, followed by recrudescence, acute yellow atrophy, and death.

Medication: Salicylates; no chrysotherapy.

CASE 22.—A girl, aged 3½ years, with painful knee since bumping it against a door two months before. An x-ray was taken elsewhere and possible fracture diagnosed. After wearing a cast for one month, the child was unable to walk. Admission examination revealed a thin, acutely ill Negro girl. Teeth were in poor condition. Heart examination revealed only tachycardia. There was swelling of the right knee and ankle. Laboratory data: Red blood cells, 3,700,000; white blood cells, 13,800; erythrocyte sedimentation rate 70 mm. in one hour. X-ray: No evidence of recent fracture.

Course: Fever controlled with aspirin. Patient transferred to contagious hospital unimproved, because she developed measles on the ward. She was then discharged improved, only to have a flare-up of pain in left knee and rise in erythrocyte sedimentation rate. A full course of gold therapy was given with no response. Because of continued activity the patient was admitted to an institution for chronic care. The arthritis progressed; a tonsillectomy was done and a second course of gold given with no response.

At present the child wears splints and is on a Balkan frame to correct a lordosis. Erythrocyte sedimentation rate is 39 mm. in one hour. X-rays are typical of rheumatoid arthritis. Contractures and deformities keep her from any useful occupation at present.

Impression: Definite juvenile rheumatoid arthritis with poor response to therapy.

Medication: Chrysotherapy.

CASE 24.—A boy, aged 6 years, developed arthritis two and one-half years before, following a bout of tonsillitis and spiking fever. Physical examination revealed a poorly nourished boy with polyarthritis, including stiff neck, generalized glandular enlargement, hepatosplenomegaly, and soft systolic murmur. Laboratory data of note were leucocytosis ranging from 15,000 to 36,000 and x-rays consistent with rheumatoid arthritis. The patient was given transfusions and vaccine therapy and was slightly improved. Check-up in a year showed progression of joint changes, however. The patient was returned to the care of his local physician and vaccine was continued (total amount received not known).

Nine years later he was admitted to another hospital because of discovery of albuminuria. He died in uremia within four months at the age of 16 years. Pathology report showed chronic adhesive pericarditis, chronic fibrous pleurisy, chronic myocarditis and mitral endocarditis (rheumatic type), amyloidosis of kidneys.

Impression: Definite long-standing rheumatoid arthritis ending with amyloidosis and death. (There are reports of the association of rheumatoid arthritis and amyloidosis, and a high percentage occur in cases where the onset was before the age of 12.4, 19 An association with vaccine therapy has been suggested but not proved.<sup>19, 20</sup>

CASE 39.—A boy, aged 8 years, with polyarthritis three and one-half months, following chickenpox and sore throat. An examination revealed a thin alert child, with enlarged tonsils



and polyarthrititis. Heart examination: Faint apical systolic murmur. Temperature, 102° to 103° F.; erythrocyte sedimentation rate 114 in one hour. Tonsillectomy in third week with rapid and constant improvement. Discharged in seventh week.

Patient readmitted in five months with fever and cough. On examination, pulse 120; temperature 104° to 106° F.; rash over entire body; heart: negative except for tachycardia. Abdomen distended and rigid; splenomegaly. Generalized glandular enlargement. Laboratory data of note: White blood cells, 20,000 to 40,000; erythrocyte sedimentation rate, 130 mm. in one hour. After transfusions, salicylates, and physiotherapy, the patient was discharged improved. He was considered to be a rheumatoid arthritic with rheumatic carditis.

On follow-up he needed splints for his hands and complained of pain in the neck. X-ray revealed a forward luxation of C<sub>2</sub> on C<sub>3</sub>.

Follow-up at age of 12 years: Tremendous appetite, is gaining too rapidly; heart is normal on physical examination. At age of 17, patient has full use of all extremities, is strong, muscular, does strenuous farm work, "is in excellent health."

Impression: Definite juvenile rheumatoid arthritis given poor prognosis because of fulminating character of illness. Later, remarkable improvement and now is entirely well.

Medication: Salicylates.

#### REFERENCES

1. Felty, A. R.: Bull. Johns Hopkins Hosp. 35: 16, 1924.
2. Still, G. F.: Med.-Chir. Tr., Lond. 80: 47, 1897.
3. Baggenstoss, A. H., and Rosenberg, E. F.: Arch. Path. 35: 503, 1943.
4. Portis, R. B.: Am. J. Dis. Child. 55: 1000, 1938.
5. Boots, R. H.: The Differential Diagnosis of Rheumatic Fever. Read before regional meeting Am. Coll. of Physicians, New York Hospital, October, 1944.
6. Colver, T.: The Prognosis in Rheumatoid Arthritis in Childhood, Arch. Dis. Childhood 12: 253, 1937.
7. Swaim, L. T., and Kuhns, J. G.: J. A. M. A. 93: 1853, 1929; 94: 1123, 1930; 94: 1743, 1930.
8. Westergren, A.: Acta med. Scandinav. 54: 247, 1921.
9. Bourn, J. M., Carpenter, H. M., and McComb, E.: Am. J. Hyg. 17: 761, 1933.
10. Coburn, A. F., and Pauli, R. H.: J. Exper. Med. 62: 129, 1935.
11. Lipman, M. O.: Personal communication.
12. Todd, E. W.: Brit. J. Exper. Path. 13: 248, 1932.
13. Nicholls, E. E., and Stainsby, W. J.: J. Clin. Investigation 10: 323, 1931.
14. Freund, J.: J. Immunol. 18: 315, 1930.
15. Baumgartner, L.: Yale J. Biol. & Med. 6: 403, 1934.
16. Hartung, E. F.: In press.
17. Taylor, G. D., Ferguson, A. B., Kasabach, H., and Dawson, M. H.: Arch. Int. Med. 57: 979, 1936.
18. Ferguson, A. B.: Roentgen Diagnosis of the Extremities and Spine, New York, 1941, Paul B. Hoeber, Inc., pp. 168 and 170.
19. Trasoff, A., Schneeberg, W., and Scarf, M.: Arch. Int. Med. 74: 4, 1944.
20. Reimann, H. A., and Eklund, C. M.: Am. J. M. Sc. 190: 88, 1935.

## EPIDEMIOLOGIC STUDIES IN DENTAL CARIES

### I. THE PATTERN OF DENTAL CARIES IN IOWA CITY CHILDREN

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MANY of the questions relating to the causation and prevention of tooth decay can be answered only through detailed and well-controlled studies of human subjects. Until the student of caries knows to what extent spontaneous variations occur in caries incidence and rates of progression in individual subjects and in given populations, he cannot appraise properly his experimental findings.

Most of the previously reported studies relating to caries incidence have been based on single dental examinations of large numbers of mouths. In some instances the data represent the composite observations of different examiners, with reasonable inference that techniques of examination and of recording were not constant. Estimates as to rates and regularity of caries progression have been based on interpolations from such cross-sectional studies, rather than from observed rates of increment. Many of the reported studies have dealt with subjects of limited geographical areas. One should not accept such studies as representative of the child population as a whole, until proved that the basic caries pattern is similar in all significant details in the contrasted localities. Contemporary studies relating to caries incidence serve better as a means of estimating tooth morbidity and mortality within a community than as a standard of prediction for findings in any individual subject.

Suitable standards for rates of caries progress cannot be deduced from cross-sectional or short-term studies of a given population, regardless of the thoroughness of such a study. Instead there is need for long-term dental studies of a large number of individual children, made with painstaking technique and constant recording method. Data as to the homogeneity of the subject personnel are also important. When the dental records can be supplemented with physical, medical, and socioeconomic data relating to each subject, the value of the study will be enhanced greatly. In the conduct of controlled studies of caries experience now under way or undertaken in the future, the methods employed should assure the utility of the data for individualized long-term study of the caries pattern.

In various institutions and clinics, data now on file could be reviewed and analyzed to aid in establishing the pattern of caries observable in the respective localities. In this institution we have at hand many serial dental records of individual children, made in a comprehensive manner and with a constant technique. Such records are available from two sources: the Children's Clinic of the College of Dentistry, and the Children's Dental Infirmary of the Uni-

From the Department of Pediatrics, College of Medicine, and the Department of Pedodontics, College of Dentistry, University of Iowa.

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versity Hospitals. We have reviewed such records, and wish in this report to present the pattern of dental caries seen in the subjects drawn from the Dental College Clinic clientele. The study is based on the records of 101 children who were examined serially not less than six times each, during an aggregate period which averaged more than five and one-half years for each child.

#### METHOD OF STUDY AND OF ANALYSIS

The files of the Children's Clinic contain dental records for more than 6,000 children. Approximately one-tenth of these records cover not less than six dental examinations for each child, and cover periods of not less than three years of intermittent observation. The first 100 such records were employed for this study.\*

The technique of dental examination and of recording has been essentially constant for the period of time the composite records cover. Preliminary to dental examination, the teeth were given thorough cleaning prophylaxis. Each tooth surface was examined minutely with fine exploring tines (SSW numbers 23 and 2); a mouth mirror was used, with good illumination. For each examination and recording from fifteen to twenty-five minutes were required. Separate records were made for each examination, without reference to earlier records until the examination had been completed. Note was made as to the presence or absence of each tooth. All clinically significant irregularities or involvements of enamel were recorded. Pits and fissures were marked non-carious unless there were good reason to believe that the adjacent dental structure had been damaged by caries. Cavities were indicated on the record as to location, extent, and activity. Extent was estimated from the area of the tooth surface involved, whereas activity was gauged by the penetrability of the underlying hard tissue by the exploring tine. Bite-wing roentgenograms were obtained routinely and were used to confirm and to supplement the clinical findings. In the current study, neither relative extent nor activity of individual lesions has been taken into account. Consideration was given instead to the number of teeth and of tooth surfaces which presented carious lesions of any type and degree. This simplified presentation is adequate for the purposes of the present review of our data.

The dental data for each separate examination were transcribed to the standard 80 column punched card designed for the mechanical sorting and tabulation of data. The values then were listed automatically from the punched cards in a variety of ways so as to permit study of the inter-relationship between caries incidence, age, sex, and other recorded factors.

The dental characteristics of the children studied have been analyzed to determine three aspects of caries advance: the incidence and extent of caries in each mouth, the observed rate of progression of decay for each subject, and the degree of regularity of advance of caries for the individual and for the group as a whole. The methodology employed for each analysis follows.

\*When analysis of the chosen records was under way, it was found that 101 subjects had been included; further, the period of observation for five subjects was less than three years, ranging from twenty-nine to thirty-four months. Inasmuch as the dental patterns of these five children did not differ characteristically from the group as a whole, their records were included in the final analyses.

1. *The Incidence and Extent of Tooth Decay in Each Mouth.*—We were interested in the total caries incidence, and consequently have given as much attention to deciduous as to permanent teeth. As a measure of caries extent, we have dealt with affected tooth surfaces rather than with the number of affected teeth. For permanent teeth, affected tooth surfaces have included those which were decayed, missing through extraction, or filled. Extracted teeth were assumed to have had three decayed surfaces prior to extraction. In the absence of other evidence, missing deciduous teeth were assumed to have been shed rather than lost because of decay. The symbol DMF has been used to express the incidence of present and of past caries, implying that the affected areas were either decayed, missing, or filled. When referring to the deciduous dentition, the symbol DF is more nearly proper, inasmuch as missing deciduous teeth were not considered in calculating the caries score. In our charts where DMF is used in reference to the mixed dentition, it implies DMF for the permanent and DF for the deciduous teeth.

2. *The Rate of Progression of Caries.*—Months rather than years have been used to measure time in this study. The age of subjects at the time of each observation was expressed in months. When the original records failed throughout to supply the date of birth but instead gave the child's age in years, the child was assumed to have been midway between the age in years stated at the earliest examination and the next subsequent year of age. The rate of progression of caries has been expressed in terms of the average number of newly acquired DMF surfaces per annum. The value was obtained by dividing the total number of such newly affected surfaces by the number of months during which they made their appearance, then multiplying this dividend by twelve. The caries progression rates have been calculated not only in terms of the total duration of observation, but also in terms of certain segments of the total when the effect of the duration of observation on caries progress was under consideration.

3. *The Degree of Regularity of Advance of Caries.*—Each child's course of observation was subdivided into those periods during which new carious lesions appeared and those periods which were free from any clinical evidence of caries progression. The rate of advance during different periods for each child has been shown graphically. The data concerning nonadvance of caries are offered for each subject in terms of the individual periods as well as of aggregate periods during which no new carious lesions were detected.

#### PRESENTATION OF DATA

1. *Nature of Subject Personnel.*—Table I lists the number, age, and sex of the subjects, the duration and number of dental observations, the intervals between successive examinations, and the state of dentition for the subjects at the initial and terminal observations in terms of chronological age.

2. *Summary of Dental Findings.*—The summarized values for caries experience in all of the subjects are shown in Table II, in terms of age and of sex. Six-hundred-and-three serial dental records are included in this summary. It is obvious that the same child's serial findings will appear recurrently in the several age categories. In this tabulation, records which were not separated by



No. of subjects Teeth present Dec. Perm. Extracted	Boys: Terminal Examination														60
	3	1	5	11	9	12	8	7	2	2	2	2	2	2	
	40	12	51	95	35	29	219	196	53	1	56	1,222	262	1,222	3
	28	10	58	160	189	203	219	196	53	1	56	1,222	262	1,222	3
			2												
No. of subjects Teeth Present Dec. Perm. Extracted	Girls: Initial Examination														41
	2	4	14	10	7	2	2								
	36	78	280	199	130	36	29								788
					24	12	16								52
															0
No. of subjects Teeth present Dec. Perm. Extracted	Girls: Terminal Examination														41
	1					7	9	6	5	5	4	3	1		
	20					73	72	36	31	4					236
						91	132	110	89	152	112	84	28		798
															0
Average Number of Teeth Present at Successive Ages: All Examinations															
AGE	Boys														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Dec.	15	19	20	20-	19	17+	14+	11+	9-	6-	3-	0	0	0	
Perm.					3-	6-	9+	11+	15-	18-	25+	27	28-	28-	
Total	15	19	20	20-	22	22	23+	23-	23+	23+	28	27+	28	27	28
AGE	Girls														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Dec.	18	20-	20-	20-	19	17-	13	10	8-	5-	2-	0	0	0	
Perm.					3	6+	10	13+	16	19+	25-	28-	28-	28	
Total	18	20-	20-	20-	22	23	23+	23+	23+	24	26+	28-	28-	28	

TABLE II. CARIES INCIDENCE IN TERMS OF AGE AND SEX

	3 YR.			4 YR.			5 YR.			6 YR.			7 YR.			8 YR.		
	N.	F.	ALL	N.	F.	ALL	N.	F.	ALL	N.	F.	ALL	N.	F.	ALL	N.	F.	ALL
Number of subjects	9	6	15	15	10	34	29	25	51	35	30	74	44	38	82	48	37	85
<b>DECIDUOUS DENTITION</b>																		
Number present	177	118	295	300	378	678	567	495	1,062	750	671	1,421	776	678	1,454	702	481	1,183
Number carious	48	40	97	71	130	201	161	175	336	231	232	463	248	281	529	202	246	538
per cent carious	27%	41%	33%	24%	34%	30%	27%	35%	31%	31%	34%	33%	32%	41%	36%	42%	51%	45%
Number of DF surfaces:																		
Mean	8.7	12.5	10.2	6.7	12.8	10.1	9.6	12.5	11.2	11.5	12.7	12.0	10.8	14.3	12.4	12.5	11.5	13.4
Range, middle ½ of subjects	2-11	3-16	3-15	2-13	4-17	3-16	2-16	5-20	2-17	6-17	3-18	3-17	9-20	6-14	6-18	9-20	6-11	6-19
Range, total	0-37	0-42	0-42	0-17	0-27	0-27	0-31	0-43	0-41	0-36	0-30	0-36	0-33	0-25	0-33	0-37	0-27	0-37
Subjects with no carious deciduous teeth	2	0	2	3	2	5	6	4	10	5	3	8	5	1	6	3	2	5
<b>PERMANENT DENTITION</b>																		
Number present	48	40	97	71	130	201	151	175	326	112	106	218	268	243	511	149	388	837
Number carious	18	15	33	21	34	55	28	26	54	32	28	60	91	115	206	152	133	285
per cent carious	37%	37%	34%	29%	26%	27%	28%	26%	27%	28%	26%	27%	34%	47%	40%	34%	34%	34%
Number of DMF surfaces:																		
Mean	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.9	1.0	1.0	0.9	1.0	2.0	3.9	3.2	1.4	5.0	5.1
Range, middle ½ of subjects	0-2	0-1	0-1	0-2	0-1	0-2	0-2	0-1	0-2	0-2	0-1	0-2	2-5	0-4	2-4	3-6	4-8	3-7
Range, total	0-4	0-7	0-7	0-4	0-7	0-7	0-4	0-7	0-7	0-4	0-7	0-7	0-11	0-11	0-14	0-20	0-16	0-20
Subjects with no carious permanent teeth	26	24	50	5	3	8	26	24	50	5	3	8	5	5	10	3	3	6
<b>TOTAL TEETH</b>																		
Number present	177	118	295	300	378	678	567	503	1,071	862	777	1,439	1,044	921	1,965	1,151	869	2,020
Number carious	48	40	97	71	130	201	151	175	336	263	260	523	330	396	735	444	379	823
per cent carious	27%	41%	33%	24%	34%	30%	27%	35%	31%	30%	33%	32%	32%	43%	37%	39%	44%	41%
Number of DMF surfaces:																		
Mean	8.7	12.5	10.2	6.7	12.8	10.1	9.6	12.5	11.2	12.4	13.7	13.0	13.4	18.2	15.6	10.9	20.5	18.4
Range, middle ½ of subjects	2-11	3-16	3-15	2-13	4-17	3-16	2-16	5-20	2-17	6-20	5-20	5-20	13-20	9-18	10-23	11-24	12-27	11-20
Range, total	0-37	0-42	0-42	0-17	0-27	0-27	0-34	0-43	0-43	0-36	0-36	0-36	0-39	0-33	0-39	0-27	0-37	0-37
Subjects with no carious teeth	2	0	2	3	2	5	6	4	10	5	3	8	5	1	6	3	1	4

TABLE II.—Cont'd

	9 YR.			10 YR.			11 YR.			12 YR.			13 YR.			14 YR.		
	N.	F.	ALL.	M.	F.	ALL.	M.	F.	ALL.	M.	F.	ALL.	M.	F.	ALL.	M.	F.	ALL.
Number of subjects	17	29	76	37	20	57	30	16	55	27	9	36	15	7	22	9	1	13
<b>DECIDUOUS DENTITION</b>																		
Number present	529	310	839	336	152	488	237	72	309	74	16	90	8	0	8	3	0	3
Number carious	273	172	445	218	89	307	145	50	195	48	14	62	5	0	5	3	0	3
per cent carious	52%	55%	53%	65%	58%	63%	61%	70%	63%	65%	88%	69%	62%		62%	61%		67%
Number of DF surfaces:																		
Mean	12.8.	13.7	13.1	13.1	8.5	12.8	8.8	9.5	9.0	3.1	3.6	3.3	0.6			0.3		
Range, middle 1/2 of subjects	8-17	3-29	7-18	9-18	5-16	3-17	5-9	3-7	3-10	0-5	0-9	0-6						
Range, total	0-28	0-37	0-37	0-25	0-31	0-31	0-24	0-20	0-29	0-25	0-12	0-25	0-10			0-3		0
Subjects with no carious deciduous teeth	0	3	3	0	3	3	0	3	3	0	0	0	0	0	0	0	0	0
<b>PERMANENT DENTITION</b>																		
Number present	515	397	912	579	310	889	714	313	1,027	614	238	852	404	191	598	248	111	359
Number carious	179	128	307	178	107	285	206	101	310	176	90	296	152	98	250	88	43	131
per cent carious	33%	32%	33%	31%	34%	32%	29%	33%	30%	27%	38%	30%	38%	50%	42%	35%	39%	37%
Number of DMF surfaces:																		
Mean	6.1	7.1	6.6	8.0	9.7	8.6	8.8	12.6	9.9	10.2	16.3	13.3	16.5	23.7	18.8	16.2	17.2	16.5
Range, middle 1/2 of subjects	1-7	5-10	4-8	5-10	7-10	5-9	5-10	6-16	5-12	4-15	10-21	5-16	7-25	21-23	8-25	12-28	18-21	12-20
Range, total	0-29	0-15	0-29	0-31	2-23	0-31	0-32	1-30	0-32	0-36	8-35	0-37	3-32	12-40	5-40	9-32	7-23	7-32
Subjects with no carious permanent teeth	1	1	2	1	0	1	0	3	1	1	0	1	0	0	0	0	0	0
<b>TOTAL TEETH</b>																		
Number present	1,074	707	1,781	915	471	1,386	951	385	1,336	718	254	972	412	191	904	251	111	362
Number carious	451	300	751	396	206	602	351	154	505	224	104	330	157	98	253	90	43	133
per cent carious	42%	42%	42%	43%	44%	43%	37%	40%	38%	31%	41%	34%	38%	50%	42%	36%	39%	37%
Number of DMF surfaces:																		
Mean	18.9	20.2	19.1	20.8	20.8	20.8	16.7	22.1	17.7	10.2	21.6	15.9	17.1	23.7	19.2	16.6	17.2	16.8
Range, middle 1/2 of subjects	13-21	12-28	12-25	15-28	15-23	13-27	9-22	12-29	10-22	6-21	16-23	9-22	7-17	21-23	8-23	12-28	18-21	12-20
Range, total	0-41	0-47	0-47	3-44	2-33	2-41	3-34	5-43	3-43	0-36	8-35	0-36	5-31	12-33	5-31	9-32	7-23	7-32
Subjects with no carious teeth	0	1	1	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0



a period of at least five months' duration were not included. Lesions of the deciduous and permanent teeth are listed separately and in combination.

Figs. 1 and 2 portray the individual long-term dental records of each subject, with separate listing of the sixty boys and the forty girls, respectively.\*

SERIAL CARES PROGRESSION IN 60 BOYS LIVING IN PRIVATE HOMES

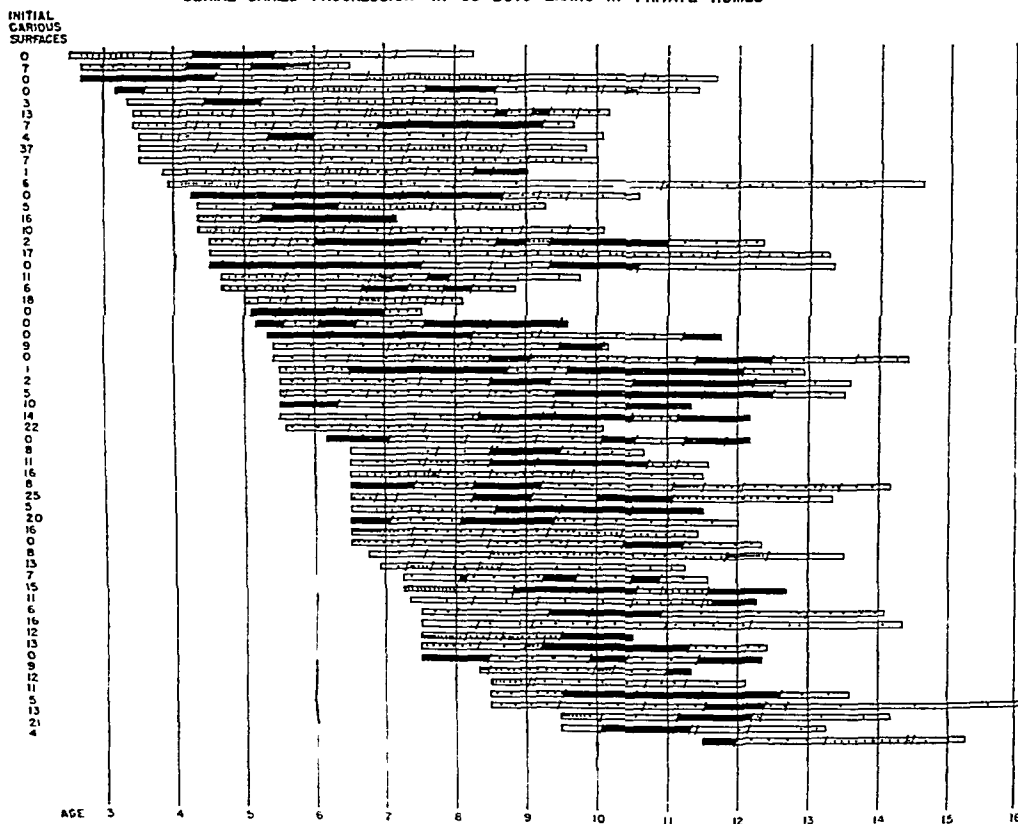


Fig. 1.—A diagrammatic representation of the serial dental status of 60 boys. Each horizontal bar portrays one subject's record. The position and length of the bar indicate age and the duration of observation. Oblique lines indicate interim dental examinations. Black areas indicate periods during which no newly carious areas were detected. The number of dots within unshaded segments of a bar indicate the number of newly carious surfaces detected at the close of the corresponding interval. The figure at the left of each bar indicates the number of DMF surfaces in the mixed dentition at the time of the earliest examination.

In these two charts, each horizontal bar represents the course of observation for an individual subject. Interim dental examinations are indicated by oblique lines through the horizontal bars; the number of newly carious surfaces developing between successive examinations are indicated by the number of dots within the segments of the bars. Areas shaded black represent periods during which no new caries was observed. The extent of caries for each child at the earliest examination is indicated by the figure at the left of each bar, expressed as the total number of affected deciduous and permanent tooth surfaces.

\*In constructing Fig. 2, the record of one girl was inadvertently omitted.

3. *Average Incidence of Caries.*—Figs. 3 and 4 portray graphically the data from Table II relating to the average incidence of carious tooth surfaces at progressive age levels. Fig. 3 indicates the average incidence of decay in both the deciduous and permanent teeth, and indicates the proportion each dentition contributes to the caries score. Fig. 4 relates to the permanent teeth only, but it indicates the proportion of the affected tooth surfaces which were contributed by lesions of the first permanent molar teeth. Of the 1,282 carious surfaces observed in permanent teeth, 800, or 62 per cent, were found in the first molars.

#### SERIAL CARIES PROGRESSION IN 40 GIRLS LIVING IN PRIVATE HOMES

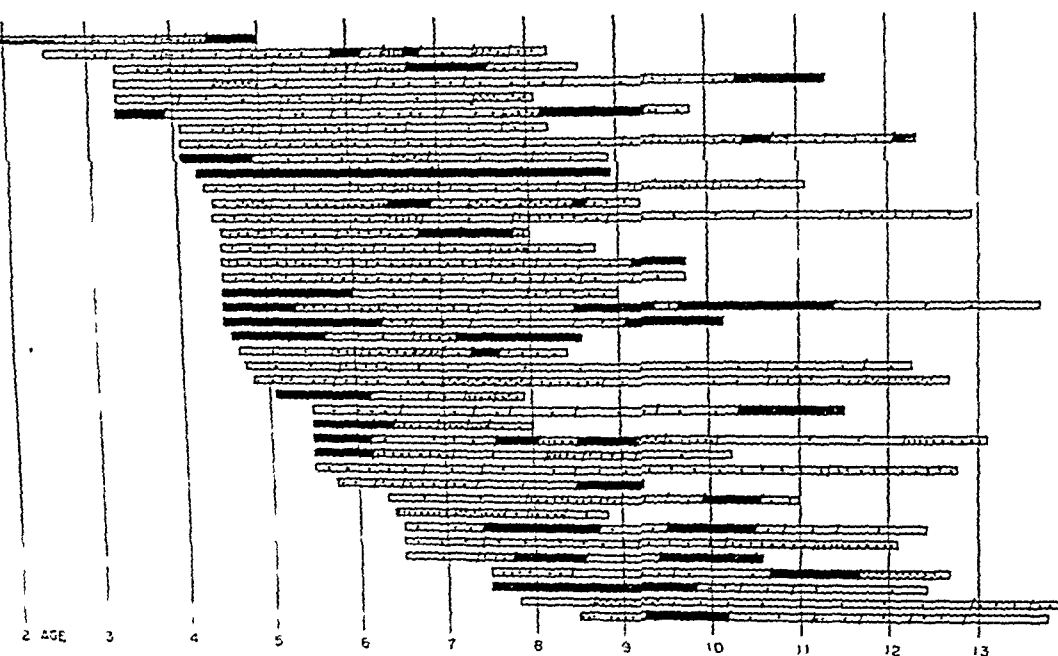


Fig. 2.—A diagrammatic representation of the serial dental status of 40 girls. The meaning of the symbols is described under Fig. 1.

The average values for caries scores do not reveal the wide dispersion of values noted in each age group. To express the predicted range of values for the middle one-half of the subjects in any age group, one should use approximately the stated average plus or minus six. The data relating to the range of values are included in Table II.

*Extent of Caries in Affected Teeth:* One may estimate the extent of caries not only on the basis of the number of surfaces affected by decay, but also from the ratio between the observed number of DMF surfaces and the number of DMF teeth. In our subjects, at the age of 6 years, this ratio averaged 1.25 affected surfaces for each affected tooth. During the following three years the ratio rose sharply to approximately 1.75:1, and oscillated near that level for the subsequent years.

*Incidence of Freedom From Caries:* Table II shows that the incidence of children who were entirely caries-free was low throughout the whole series. The proportion of those free from caries diminished rapidly with age progression; after the age of nine years, only a single child was entirely free from caries and his earlier record had shown caries of the deciduous teeth. In terms of caries incidence in relation to the total number of teeth in the mouth, it will be noted that approximately one-third of the teeth present at each age level showed decay.

DMF SURFACES, MEAN VALUES, ALL TEETH  
(VALUES FOR DECIDUOUS SURFACES ARE SHADED)

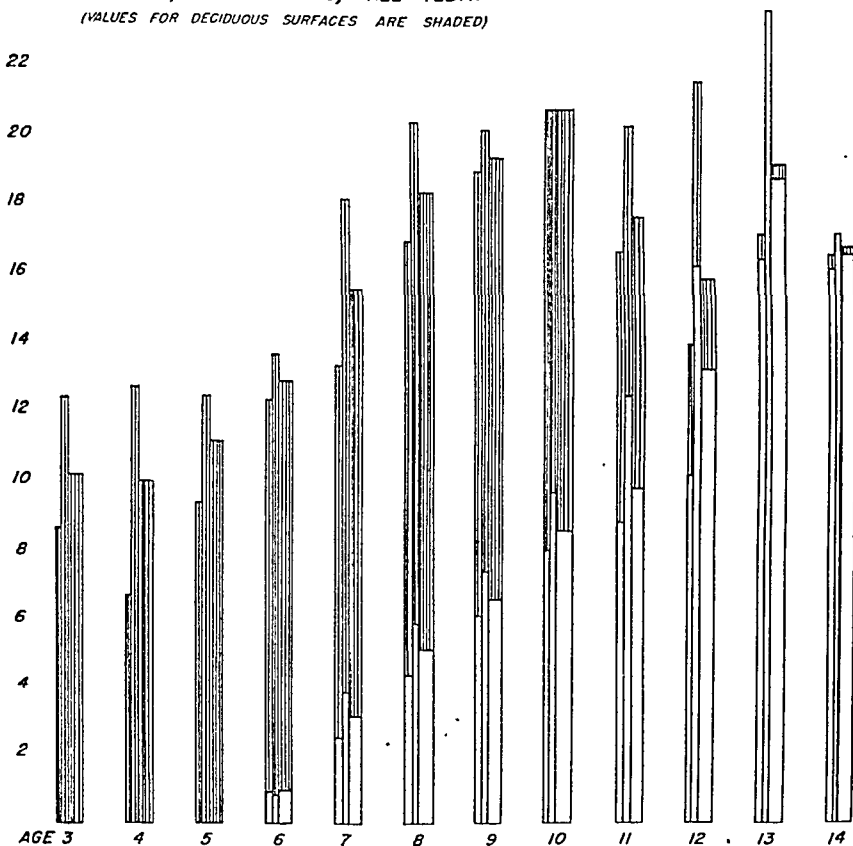


Fig. 3.—The average extent of caries in the mixed dentition at successive ages. For each age the values for boys, girls, and the combined sexes are shown, respectively, in the three columns, reading from left to right. Values for deciduous teeth are shown in the shaded areas; they are expressed in terms of the number of surfaces with decay or fillings. Values for permanent teeth include also the score for extracted teeth, each rating as 3 affected surfaces.

*Tooth Mortality:* Loss of permanent teeth through extraction was remarkably low in the whole series. Only 2 of the 101 subjects had lost permanent teeth through extraction. In one of these, two incisors had been lost as the result of a fall from a horse. The other child lost a first permanent molar which already was extensively carious the first time he was examined.

4. *Rate of Progression of Caries.*—During the course of observation, an aggregate of 2,248 newly carious surfaces was discovered: this includes 1,053

in deciduous and 1,195 in permanent teeth. Thus the average annual increment of caries was 3.83 newly carious tooth surfaces per annum; the standard deviation was 2.09, and the standard error of the mean, 0.22. These values reflect the wide variation to be observed in the individual rates. As the data will show, this deviation is notable not only from one subject to another, but for the same subject at different segments of his course of observation. The dispersion of values is shown in Figs. 1 and 2, and in the various parts of Fig. 5.

5. *Variability of Rate of Caries Progression.*—Fig. 5 deals with the frequency distribution of the individual rates of annual caries increment among

*D M F SURFACES, PERMANENT TEETH, MEAN VALUES*

24 (VALUES FOR FIRST MOLAR SURFACES ARE SHADED)

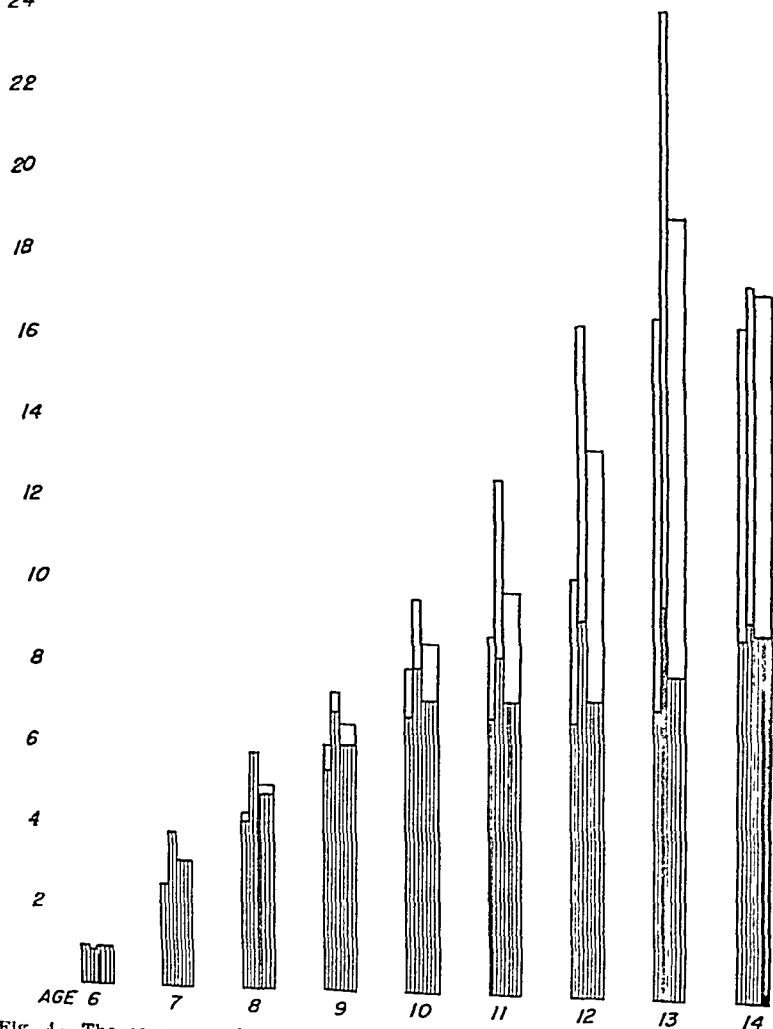


Fig. 4.—The average extent of caries in the permanent teeth at successive ages. For each age the values for boys, girls and the combined sexes are given, respectively, in the three columns, reading from left to right. Values are expressed in terms of the number of affected surfaces, as described under Fig. 3. The number of affected surfaces found in the first permanent molars is indicated by the length of the shaded portion of each column.

the subjects throughout the periods of observation. Each of the bars in Fig. 5 shows the median increment rate, together with the range of values observed in the middle one-half, and in the outer tenths of each group. Fig. 5 is subdivided into sections numbered serially from 1 through 4, each section relating to different groupings of the subject personnel.

NEW DMF SURFACES PER ANNUM: DECIDUOUS AND PERMANENT TEETH  
RANGE AND FREQUENCY DISTRIBUTION OF INDIVIDUAL AVERAGE VALUES

SECTION 1

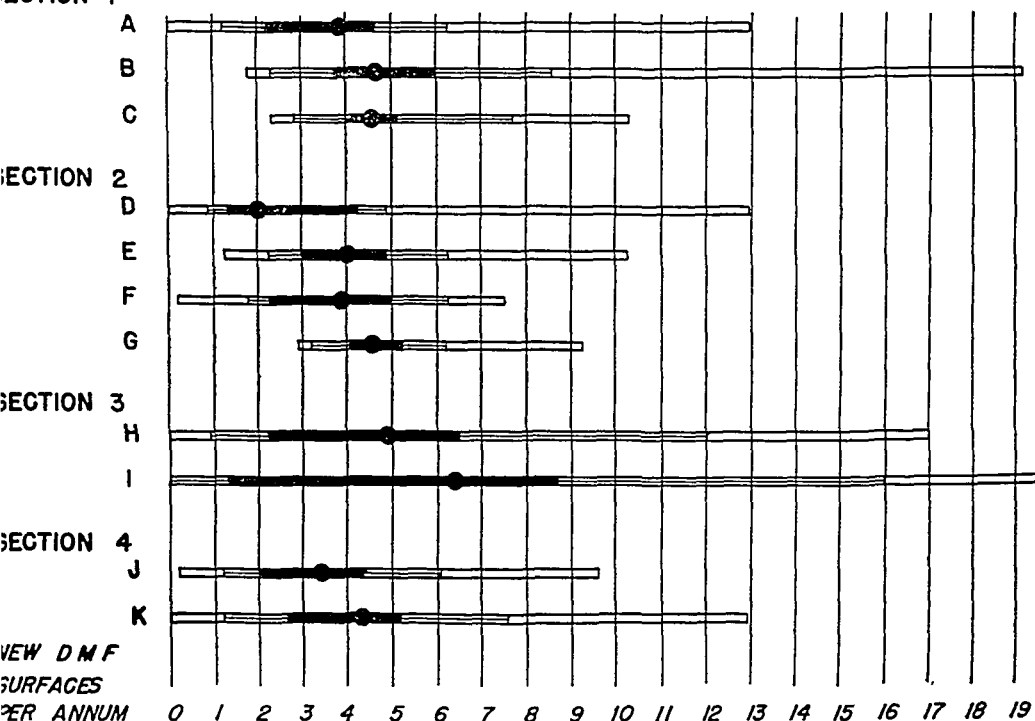


Fig. 5.—Frequency distribution of caries increment rates (the average number per annum of newly carious surfaces in the mixed dentition for each subject). Bar A represents the range of values for the whole group of subjects throughout the total duration of individual observation. The remaining bars deal with various segments, both of the subject personnel and of the duration of individual observation, as defined in the text.

In each bar, the black circle indicates the median value. The zone shaded black represents the range of values for the middle one-half of the subjects. The unshaded zone represents the range of values observed among the outer tenths of the respective group.

*Over-All Rate of Caries Progression:* (Section 1) Bar A shows the rates of caries increment observed among the whole group of subjects throughout the total duration of observation periods. It indicates that the individual whose average annual rate of caries increment placed him midway between the child with the lowest and the child with the highest rates had an average increment rate of 3.8 newly carious tooth surfaces for each year of observation. Further, it shows that one-half of the total group had average increment rates which ranged between 2.2 and 4.7 new DMF surfaces per annum; that 10 per cent of the group had values which ranged from none to 1.3, whereas another one-

tenth had values ranging from 6.2 to 12.9. Bar *B* offers similar data, but in it the total period of time used in estimating the average increment rate did not include those periods during which no new caries developed (represented as the black segments in Figs. 1 and 2). Bar *C* includes only those subjects who showed no periods during which caries had not advanced.

*Relation of Increment rate to Earlier Incidence of Caries:* Section 2 of Fig. 5 shows the relationship between the initial extent of caries in the individual mouth and the subsequent average rate of caries progression. The subjects were arranged in order of their initial caries scores (left-hand columns, Figs. 1 and 2) and then divided into fourths. The rate of average caries progression is shown separately for each one-fourth of the total group in bars *D*, *E*, *F*, and *G*, relating, respectively, to those with the lowest through to the highest initial caries incidence.

In Section 3 of Fig. 5, the middle one-half of subjects (those portrayed in bars *E* and *F*) have been subjected jointly to further analysis to determine the effect of the duration of observation period on the average rate of caries progression. The middle one-half was chosen for this analysis in preference to the total subject population, so as to portray more closely the response one may expect in the average child rather than in either outgroup. In bars *E* and *F*, the range was expressed in terms of the total duration of observation for each subject. In bar *G*, only the initial year or two of observation was used in calculating the individual average annual caries increment. In bar *H*, only the interval between the first and second dental examinations was used in computing the average increment; further, only those subjects are included whose intervals between the first and second examinations ranged between 3 and 11 months.

Sections 1, 2, and 3 of Fig. 5 are based on the combined values for the two sexes. Section 4 presents the ranges of observed values for boys and for girls separately. Bars *J* and *K* correspond with bar *A* as to the subjects included and as to the duration of observation. The differences will also be discussed.

Reviewing the substance of Fig. 5 as a whole, it is apparent that caries of the mixed dentition progressed in the representative subject at the average rate of almost 4 newly affected surfaces per annum, even though the subjects were under recurrent dental care. The average increment rate was least among those children who initially had the least caries experience, and highest in those whose early caries experience had been the greatest. The shorter the period of observation, the higher the average increment rate: when the period of observation did not exceed 11 months, the median rate noted was almost  $6\frac{1}{2}$  newly carious surfaces per annum. The median average rate for boys was less than that for girls: 3.4:4.3. The corresponding arithmetical means show a corresponding and statistically significant difference. The lack of homogeneity of findings, evident even within the subgroups, is illustrated by the variable range observed in the middle one-half of the subjects. Those who initially had the highest caries experience (bar *G*) showed the greatest homogeneity (the smallest range of values), whereas the group with the least caries at the beginning (bar *D*) showed the greatest inconstancy among its constituents as to increment

rates. The degree of dispersion increased greatly when the total periods of observation were segmented, as illustrated in bars *H* and *I*.

*Significance of Sex Differences in Increment Rates:* In view of the sex distinctions noted, further studies were made to rule out the possible effect of chronological and of dental ages on the observed differences. Table III shows the observed average annual caries increment rates for boys and for girls at successive ages from 5 through 13 years. With but two exceptions, the average values were consistently and notably higher for girls than for boys not only for respective years but throughout the total age span studied. Our data relating to caries progression in terms of posteruptive tooth age will be presented in another report; the trends observed will be discussed subsequently in this presentation.

TABLE III. AVERAGE ANNUAL CARIES INCREMENT RATES IN TERMS OF SEX AND OF AGE OF SUBJECTS (DMF SURFACES PER ANNUM)

AGE RANGE	5 TO 6	6 TO 7	7 TO 8	8 TO 9	9 TO 10	10 TO 11	11 TO 12	12 TO 13
Boys	3.9	3.2	3.7	3.4	3.7	3.1	2.9	2.9
Girls	4.1	4.0	5.8	4.8	3.9	4.1	2.8	4.5

*Inconstancy of Successive Annual Caries Increment Rates for the Given Individual:* The foregoing analyses reflect the variability of caries advance among the different subjects. Similar variability was noted during the course of observation of the individual subject. This is apparent from Figs. 1 and 2. Further analysis was made to determine the degree of constancy of the individual's percentile rating of caries extent observable at the time of his serial examinations. To offer the greatest possible number of subjects for the analysis, 8 years of age was chosen as the age of reference. Children whose total caries incidence at that age placed them in the middle one-half of the group were studied as to their quartile position for caries extent at 6 and at 10 years of age. Sixty per cent of those in the middle one-half of the group at 8 years of age were also in that range at 6 or at 10 years of age, or both. The remaining 40 per cent were about equally divided between the first and fourth quarters of the group. Such distribution corresponds to what one would expect to find through factors of chance in any population. Moreover, the range of values encompassed by the middle one-half of the group is so wide that little homogeneity exists within that group. These ranges were from 5 to 20, 12 to 27, and 13 to 27 DMF surfaces at the respective ages of 6, 8, and 10 years.

The inconstancy in the regularity of advance of caries in the individual subject can be illustrated further, through consideration of the duration of nonadvance of caries in the individual subjects. In the aggregate, extension or initiation of caries was noted during 5,271 of 6,839 months of observation in our 101 subjects. This represents about 73 per cent of the time. Of the 1,568 months during which no advance of caries was detectable, 1,180 months represented consecutive periods, whereas the remainder comprised intermittent segments of variable duration interspersed with periods of advancing caries. Approximately 90 per cent of the cumulative consecutive nonadvance was made up of periods of more than 10 months each. Periods of such length were ob-

served in more than one-half the total number of subjects. The subjects grouped themselves essentially into fourths in regard to their demonstrable nonadvance of caries. About one-fourth showed no period of nonadvance of any duration; newly carious surfaces were demonstrated at the time of each recurrent examination. Another one-fourth had periods aggregating less than 12 months with no caries advance. One-fourth had periods ranging from 12 to 24 months with no caries advance, and the remaining one-fourth were clinically free from advancing caries for periods of two years or longer. Prolonged nonadvance (12 months or longer) was observed at some stage of observation in 60 per cent of the boys, but in only 42 per cent of the girls.

#### DISCUSSION

This study was designed to serve as a background for future investigations concerning caries control. Before studying caries progression in children living under imposed environmental conditions, it is important to know the predictable response when no control has been imposed. For economy and efficiency of effort, the experimenter should know the degree of deviation to be expected in an uncontrolled group, and recognize the factors which may lead toward deviant results. From such knowledge he can determine more nearly adequately the number of subjects and the duration of observation needed to assure validity to his data. Working toward these objectives in the current study, it was necessary to devise a pattern for the study of caries experience based on long-term examinations of individual children in contrast to the commoner technique of using cross-sectional observations without maintaining the identity of the individual subjects. Because our subject personnel included children in various stages of dentition, it has been necessary to employ techniques which portrayed caries progress both in the deciduous and the permanent dentition. The method employed seems adequate for the purpose.

From a review of our data, one may characterize the caries course of our subjects as follows:

1. Caries was practically universal among the members of the group.
2. Practically without exception, caries tended to progress during the periods of observation.
3. Recurrent dental care did not halt the progression of caries, but it served to prevent the loss of teeth.
4. The rates of progression of caries differed widely among the different subjects, and in the same child from time to time during the individual periods of observation. Data are not available to permit thorough analysis of the reason or reasons for this fluctuation in rates of caries extension. Some of the recognized constants and variables which characterized the environment of the subject population will be discussed later.
5. The serial course of caries progression for the individual child is not portrayed through the average values for caries in terms of age or sex, or by the average rates for caries progression. Only through individualization of long-term dental records was it possible to picture the pattern of caries in the individual subject.



Is the volume of data sufficient to define the caries characteristics of a population? Such a question is relevant, in view of the inconstancy of the data. As a measure of the incidence of caries for children of given age and sex, many more values would be desirable. It is especially regrettable that our data do not include many values for children in their teen years. From the viewpoint of annual caries increment, however, it seems doubtful whether greater accuracy would be obtained from larger numbers of subjects. Surely the average duration of observation for each child and the minimum number of dental examinations in each record are sufficient to insure accuracy of record and of observation for each child.

To learn the effect of the size of sample and the duration of observation on the average results obtained, we have compared the average response for the group as a whole with the corresponding average for segments of the total population studied, and for segments of the total periods of observation. In part, this was presented in the preceding section. Without stating the results in detail, it may be said that the number of subjects could be reduced by one-half or even more, without introducing serious deviation from the whole group average for caries increment rate. On the other hand, when the increment rate was determined using fractions of the total periods of observation, great inconstancy of the average increment rate was obtained. It became apparent that little could be deduced of an individual's average long-term increment rate through values from observation periods of less than six months. Further, it seemed doubtful whether such short periods of observation would be sufficient to reflect clearly any change in caries propensities, such as might be attributed to imposed experimental conditions. Until more is known of the latency of development of caries lesions, it will be well to assume that several months are necessary to make apparent any potentialities for caries advancement or retardation, using the usual clinical methods of appraisal.

Caries increment rates determined for intervals of approximately one year's duration showed greater constancy than for shorter intervals, but tended to a higher average value than when a still longer period was used as a basis for calculation. For practical purposes we believe that a year of recurrent observation of the given subject would provide a valid estimate of his current caries propensities. From a group of about thirty individuals so studied, one should be able to deduce statistically valid estimates as to caries progression rates during an equal period for a larger similar population. For economy of effort and for coherence of results, we believe that the ideal experimental or control group of children would be of the same sex and age, and of similar caries experience prior to the projected study.

Aberrations in rates of caries progression between different children may be due to various factors, acting separately or in combination. Some such factors could explain the variable rate seen in a given subject at different periods of his observation. If one may assume that the child's caries pattern will reflect his manner of living, then one would expect that with the passage of time and season, and with changes either in the child's practices of eating, his level of health, or in other matters relating to hygiene, his current rate of caries pro-

gression might fluctuate. If our subjects had lived under imposed conditions of regimentation, their caries progression rates might well have been less erratic. In a study similar to the one herein reported, but dealing with the caries course of diabetic children, there was but slight progression of caries in any subject, and the degree of deviation both for the individual and for the group as a whole was minimal.<sup>1</sup> Those children were living under conditions much more nearly regimented than is possible to obtain with the usual child population.

We have no data of the diet habits of the children used in this study, but we may infer that they were as diverse as in any similarly uncontrolled group of children, and that suboptimal intake of specific nutrients was prevalent.<sup>2</sup> We recognize and wish to emphasize that we have studied a picked group of children, chosen from the clientele of a dental clinic. Such sampling, of itself, would affect our quantitative results. One must not assume, however, that these children had come to the clinic primarily because of their dental needs. Many of them came as a part of the "Iowa Dental Plan," in accordance with which each school child is asked by the school authorities to take a card to his dentist annually and have the dentist certify either that no dental therapy is needed, or else that the necessary services have been performed. Children with minimum dental needs might be expected to report with less regularity than would children with symptoms referable to the teeth. Possibly the general school population would have included an appreciably larger proportion of children who were free from caries.

Has fluoride ingestion played a significant part in the caries experience of these children? Probably the children used in this study have received insignificant amounts of fluorides from the domestic water supply. Most of the subjects had been born in Iowa City and had lived there continuously. Iowa City receives its water supply from the Iowa River, after the raw water has been filtered through galleries and then clarified. Whereas as much as 2 parts per million of fluorine has been reported from wells used by the University for industrial purposes, the domestic water supplies for the community have been reported fluorine-free or to contain at most a trace.<sup>3</sup> Probably from the evidence at hand, it would be generally agreed that the water as consumed in this locality does not contain sufficient fluoride to affect caries control significantly.

To what degree do the reported dental findings relate to the child population at large? Our data portray the pattern of caries progression in a specific group of children. One should not infer that the data would apply equally well in their quantitative aspects to the average Iowa school population, until our findings have been compared with such a population. However, even though our subjects may not necessarily represent a community average, this does not lessen the value of their individual records for study. The caries course as exemplified by a given subject can be used as a basis for comparison with the course of other children of similar description. Conclusions, as they relate to the manner of progression of caries, should be valid for children from any group or locality.

For general comparison, the data from Klein and Palmer's<sup>4</sup> study of children from Hagerstown, Md., have been employed. Their study was thorough and comprehensive, made with a constant examining personnel, and dealt with children of a community similar in many respects to Iowa City. The notable distinction between the studies is that theirs is cross-sectional, based on a single examination of each mouth.

TABLE IV. STATUS OF PERMANENT TEETH OF CHILDREN FROM DENTAL CLINIC COMPARED WITH THAT OF CHILDREN FROM HAGERSTOWN, MD.<sup>4</sup>

	CHILDREN FROM DENTAL CLINIC	HAGERS- TOWN SCHOOL POPULATION
Number of permanent teeth present, aggregate of terminal examinations	2,012	
Number of these with DMF lesions	695	
Proportion of teeth which were carious	35%	15%
Number of surfaces with DMF lesions, aggregate of terminal examinations	1,282	
Average number of DMF surfaces for each DMF tooth	1.85	1.93
Average incidence of DMF surfaces for each child at terminal dental examination:		
(Average age, Iowa City children, 130 months)	6.9	
(Average age, Hagerstown children, 125 months)		5.5
Proportion of DMF surfaces located in first permanent molar teeth	59%	78%
Incidence of extracted permanent teeth:		
Proportion of children who had lost one or more permanent teeth	2%	18%
Ratio of extracted teeth to DMF teeth	0.04%	10%
Average annual increment of DMF surfaces:		
Dental clinic (observed)	2.7	
Hagerstown value (computed)		1.3

Table IV offers a summary contrasting the Iowa City to the Hagerstown studies. From that table it is evident that our subjects had the higher average caries incidence rate for permanent teeth and the more rapid apparent rate of caries progression. It will be recalled, however, that in the Hagerstown study the stated increment rate was calculated through interpolation rather than observation. The average apparent extent of caries in the average affected tooth is similar for each group, in so far as the extent of caries can be measured from the number of DMF surfaces alone. However the incidence of extracted teeth is notably higher in the Hagerstown group, this implying at first glance that the severity of caries or its steadiness of progression had exceeded that in the Iowa City subjects. The lesions found in the first permanent molars by Klein and Palmer comprise a much higher proportion of the total lesions than was found in the Iowa City children. This distinction may be more apparent than real, dependent on the manner of weighting the values for extracted teeth in the Hagerstown study. Klein and Palmer assumed that each extracted permanent tooth had experienced caries in all five exposed surfaces prior to extraction, and scored such teeth accordingly. If such teeth had remained unextracted and untreated, the DMF score might have been considerably less than their estimate. Possibly the actual extent of destruction of first molar teeth in the contrasted series of children was not greatly different, because the incidence of extraction may reflect the type of dental care their subjects had received.<sup>5, 7</sup>

If the incidence of DMF surfaces for permanent teeth in the Hagerstown children is less than has been estimated by Klein and Palmer, then the disparity between the DMF scores in the Iowa City and the Hagerstown groups becomes still greater than already has been pointed out.

The examining techniques employed by Klein and Palmer were basically the same as those used routinely in our Children's Clinic. Important, however, is the fact that the Dental Clinic examinations were preceded by a thorough prophylactic cleaning of the teeth. In the absence of such preliminary cleaning, and with shortening of the examination period, one would expect to miss some of the smaller dental lesions.

During the summer of 1944, we had an opportunity to compare dental records made in the course of a general school survey with records of the same mouths made concurrently by our own dentist.\* The routine school examination for each child was completed in less than five minutes, whereas our examiner required from fifteen to twenty-five minutes for each examination and its recording. In other respects the techniques of examination were comparable. The DMF scores for individual children varied widely in the two examinations, often by as much as 100 per cent, and averaged 50 per cent higher for the longer examination procedure.<sup>6</sup>

From the data as they stand, we conclude that the Iowa Dental Clinic group of children had a higher incidence of caries than did the Hagerstown group, but that the individual dental lesions were less severe and that tooth mortality was much lower in the Iowa city group. One would expect the higher incidence of minor lesions with the technique employed. The relationship between the mortality of teeth and the degree of dental service received earlier by the examined group will be discussed elsewhere.<sup>7</sup> It is reasonable to attribute the low loss of teeth in the Iowa City subjects to the recurrent dental therapy.

The girls of this series had significantly higher incidence of carious surfaces than did the boys. Klein and Palmer made similar observations, and attributed the distinction to the fact that at a given age girls are more precocious than boys in the time of eruption of teeth, and consequently the teeth have been exposed to caries-promoting agencies in the mouth for longer periods of time. They concluded that girls as a sex show no greater susceptibility to caries than do boys.<sup>8</sup> Our data indicate that the girls as an average not only had more caries than boys at given age levels, but also that they had higher average caries increment rates than did the average boy. Unpublished data from this study show that the same distinction prevails when one studies the rate of advance of caries in first permanent molar teeth, basing calculations, not on the chronological age of the subject but instead, on the number of months which had elapsed following the appearance of four first permanent molars in the mouth of each individual subject. The apparent sex difference in caries pattern is illustrated in this study through data from Tables II and III, in Figs. 1 and 2, in bars J and K of Fig. 5, and in the lessened incidence of periods of nonadvance among girls which was cited in the last paragraph of the section on presentation of

\*Dr. Wah Leung, whose services were made available to us through the courtesy of Dr. Harold Hodge of the University of Rochester and the Carnegie Corporation.

data. We do not imply that tooth age does not play a part in the likelihood of caries progression. Moreover, we believe that there is no established and inherent tendency for girls to tend toward greater caries experience than boys. Our data make it necessary, however, to supplement the tooth age concept as a predisposing factor toward caries with added theories as to why one sex tends to show more rapid progression of caries. One may postulate that as a group, girls are inclined to give less consideration to good habits of eating than are boys. Our observations support such a concept, and lead us to believe that advance of caries is favored by such dereliction. With regimentation of eating habits, sex distinction in caries progress was not noted among diabetic children.<sup>1</sup>

#### SUMMARY AND CONCLUSIONS

The long-term course of dental caries in a large group of children has been presented. Caries was practically universal in the members of the group, and the tendency to progress with the passage of time likewise was almost universal. The average rate of increment approximated four tooth surfaces per annum. The loss of teeth through decay, however, was negligible. Prevention of tooth mortality may be credited to the recurrent dental service the children were receiving. It is significant that such dental therapy did not prevent initiation of new areas of decay. The serial course of each child's caries was erratic, typically being interrupted by intervals during which no new advance could be detected. The nature of the data emphasizes the need for long-term studies of caries progression in individual children as a measure of effectiveness of caries control, in contrast to the cross-sectional methods of caries survey which have been commonly employed.

#### REFERENCES

1. Boyd, J. D.: *Am. J. Dis. Child.* 66: 349, 1943; *J. Am. Dent. A.* 30: 1344, 1943.
2. Boyd, J. D.: *J. Am. Dietet. A.* 20: 147, 1944; *J. PEDIAT.* 24: 616, 1944.
3. Iowa State Planning Board, *Mineral Analysis of the Underground Waters of Iowa*, State Printing Board, 1938, et seq.
4. Klein, H., Palmer, C. E., and Knutson, J. W.: *Pub. Health Rep.* 53: 751, 1938.
5. Cheyne, V. D., and Drain, C. L.: *J. Dent. Research* 19: 571, 1940.
6. Boyd, J. D., Cheyne, V. D., Leung, W., and Hoffman, O. D.: Unpublished data.
7. Boyd, J. D., and Cheyne, V. D.: Unpublished data.
8. Klein, H., and Palmer, C. E.: *Pub. Health Rep.* 53: 1685, 1938.

## THE INFLUENCE OF HUMAN SERUM ALBUMIN ON EDEMA IN ERYTHROBLASTOSIS FETALIS

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THE TREATMENT of erythroblastosis fetalis has become important with the more general recognition of the disease in recent years and under the stimulus of increasing knowledge of its pathogenesis. Routine typing of expectant mothers for the Rh factor has resulted in earlier diagnosis of the disease and in more effective therapy.<sup>1</sup> The treatment has been, for the most part, aimed at combatting the anemia by means of blood transfusions; there has been no attempt directed specifically at the reduction of the marked edema present in the majority of the more severe cases. Wiener and his co-workers<sup>2</sup> clearly state this, "Blood transfusions are not the complete answer to the problem of the treatment of hemolytic anemia of the newborn, even when the infants appear to be in good condition at birth. Transfusions are merely a substitution therapy and therefore save only those infants who would otherwise die from extreme anemia brought about by the destructive action of the maternal isoantibodies." It has never been shown that anemia is the most important cause of death. In a recent review of 58 cases, Leonard<sup>3</sup> has shown that fatalities occurred in infants treated by transfusion who had hemoglobin values, on admission, from 9 to 23 Gm., with an average of 13 Gm. A study of her statistics shows 6 of 12 infant deaths with clinical edema, and the author clearly points out that, "Marked edema is . . . recognized as a grave prognostic sign."

We have had similar experience and have felt that the edema is not due to anoxemia, as is the commonly accepted belief, but is, rather, associated with a lowered osmotic pressure because of low blood protein levels. This would be expected as a result of the liver damage found so regularly, particularly in the more severe cases of erythroblastosis fetalis. We recently had the opportunity of treating empirically, with concentrated human serum albumin, one of twins presenting severe generalized edema incident to marked erythroblastosis. The treatment was undertaken as a last resort and proved dramatically efficacious in reducing the edema after previous transfusions had failed entirely in this respect, and eventuated in the infant's complete recovery. His twin sibling, given only transfusions, died 54 hours after delivery even though the clinical and laboratory evidences of erythroblastosis were milder than in the serum albumin-treated child.

We subsequently treated another case, of erythroblastosis fetalis complicated by marked pitting edema with the same excellent results. Biochemical studies in this case indicate that the edema occurred when there was a fall in the blood protein level, and that this fall was corrected by the administration of the serum albumin. With the restoration of the blood proteins the edema

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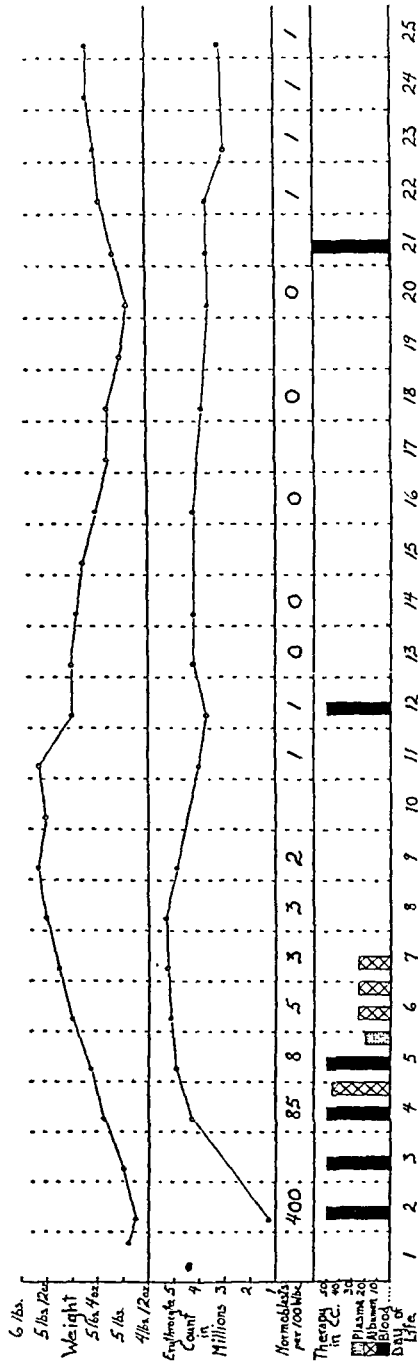


Fig. 1.—Course of Infant B (Case 1).

disappeared. Positive cephalin flocculation tests and a markedly prolonged prothrombin time were indicative of severe liver damage.

#### CASE REPORTS

CASE 1.—Male twins were born to Mrs. F. C. at 11:55 P.M. on Dec. 7, 1945. The first child weighed 4 pounds 15 ounces, and the second, 5 pounds 10 ounces. The following morning both infants were markedly jaundiced. An enlarged liver and spleen could be palpated in each child. We shall designate the first and smaller infant "B," and the second and larger infant "A," for that was subsequently found to be their blood types. Both infants were Rh positive. The mother was type AB, Rh negative. The father was type O, Rh positive.

Initial study of the infants' blood showed the following:

	B	A
Hemoglobin	7 Gm.	14.5 Gm.
Erythrocytes	1,250,000	4,100,000
Leucocytes	400,000	35,000
Normoblasts per 100 Wbc	400	9

Each child was immediately given a transfusion of 50 c.c. of compatible Rh-negative whole blood.

The following day it was noted that the jaundice had increased in both babies and, more importantly, both had developed marked generalized edema. Baby B had gained 2 ounces and Baby A had gained 5 ounces. The legs, arms, and scalp were puffy and could readily be pitted. The edema and the jaundice gave the infants a waxy appearance. Baby B was again given a transfusion of 50 c.c. of whole blood, but transfusion was temporarily delayed on Baby A because of his initial high hemoglobin and red cell values. As the day progressed, Baby A became somewhat dyspneic and bubbling râles were heard in the lungs. He was again transfused, but despite the transfusions, and the use of continuous carbogen, he expired fifty-four hours after birth. At the time of death this infant manifested marked generalized edema, the arms and legs being approximately twice their initial circumference. There was marked pitting of the extremities, back and scalp.

On the morning of the third neonatal day, the surviving infant, Baby B, manifested a greater degree of jaundice and edema, though the blood count revealed a rise in hemoglobin to 14 Gm., a drop in white cells to 40,000, and a drop in normoblasts to 85 per 100 white cells. (Fig. 1 shows this and subsequent studies.) The child was again transfused, but the edema became more marked. He became dyspneic, and râles were heard. At this point the infant looked far more edematous than had his twin.

It was realized that transfusions were obviously of no value in combatting the edema, and it was decided to attempt to dehydrate the tissues by a transfusion of concentrated human serum albumin.\* The infant was given 45 c.c. of the serum albumin, containing 11.25 Gm. of albumin. Within six hours a very pronounced diminution in the edema was noted. The veins of the extremities, previously not visible, could now be seen, and the pitting was slight.

The following morning the edema had recurred, though not to as marked a degree, and the infant had gained an additional 2 ounces. Another transfusion of 50 c.c. of whole blood was given and, there being no more available serum albumin at the moment, the child was given 20 c.c. of five times concentrated dried plasma. No appreciable effect could be noted following this therapy.

On the morning of the fifth day the edema was found to be still greater and on the order of that before the initial use of serum albumin. The child had gained 3 ounces. Twice that day and once again on the sixth day he was given 6.25 Gm. of the now avail

\*The human serum albumin was kindly furnished by Dr. Charles Janeway of the Boston Children's Hospital.



able human serum albumin. Although he continued to gain weight for several days more, the edema rapidly diminished so that by the seventh day it was barely perceptible and was totally gone by the ninth day. No pitting was demonstrable, and the extremities were not at all swollen. The liver was still enlarged, the spleen barely palpable. A supportive transfusion of whole blood was given on the eleventh day.

The infant showed a slowly diminishing residual jaundice. The liver and spleen were no longer palpable and there was no edema. There were no positive neurological findings. He was vigorous, had a lusty cry, and gained weight. Normoblasts were no longer present in the peripheral blood, the components of which were those of a completely normal newborn infant.

**CASE 2.**—M. K., a white male was born at 11:55 P.M. on Feb. 8, 1946, of an Rh-negative mother. The vernix and amniotic fluid were noted to be yellow at the time of delivery although the infant was not jaundiced. Within twelve hours, however, the child was markedly icteric and the liver and spleen were found to be enlarged. The peripheral blood revealed 82 nucleated red blood cells per 100 white blood cells, 16 Gm. hemoglobin, 3,660,000 red blood cells, and 49,000 leucocytes.

He was immediately given a transfusion of 65 c.c. of Rh-negative whole blood, and this procedure was repeated on the second day of life.

On the third day he had gained 3 ounces and there was periorbital edema as well as edema of the scalp, hands, legs, and feet. He was given a third transfusion, but despite a good hematological response, he continued to become more edematous.

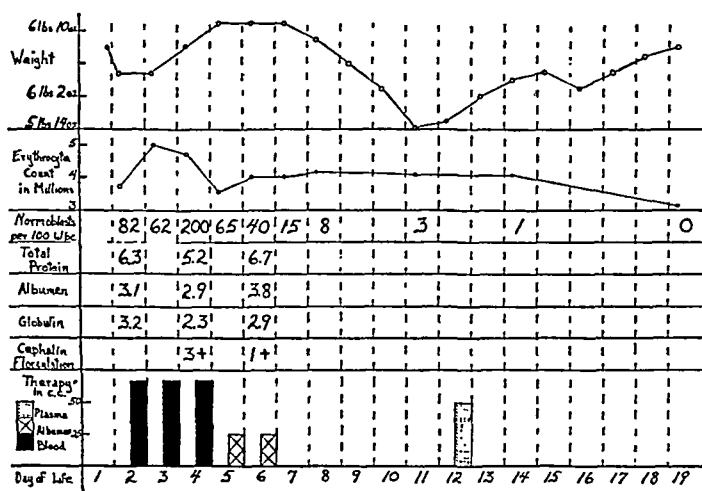


Fig. 2.—Course of infant M. K. (Case 2).

On the fourth day he had gained an additional 3 ounces and there was now a marked pitting edema of the entire body. At this time he was given 6.25 Gm. of concentrated human serum albumin intravenously. There resulted a marked diminution of the edema within six hours. As an index, it was noted that there was a one-half inch decrease in the circumference of the legs.

The next morning the edema had reappeared, but not to the extent of the previous day. The weight remained stationary. He was again given 6.25 Gm. of concentrated human serum albumin and by the following day there was no apparent edema. The eyes, which had previously been so puffy that the infant could not open them, were now wide and bright, and his jaundiced sclerae could be seen readily.

The child proceeded to make a completely uneventful recovery from his erythroblastosis. For a while he was a feeding problem, but this was only transitory. During

the fourth week of life he was given two supportive transfusions. At the time of writing he is alive and doing very well. His peripheral blood picture is entirely normal and he is completely negative on physical examination.

This patient was particularly interesting because we had the opportunity of doing various blood studies during the course of his disease. (Fig. 2.) It was noted that despite early transfusions there was a marked drop of 1.1 Gm. in the serum proteins. Along with this fall in the protein level the edema appeared and when this fall was corrected the edema disappeared. The positive cephalin flocculation test (3 plus) and a prolonged prothrombin time showed marked liver damage, and the fall in the flocculation was taken as an indication of the recuperative powers of the liver.

TABLE I. HEMATOLOGICAL COURSE OF INFANT "B"

DAY OF LIFE	HEMOGLOBIN IN GRAMS	ERYTHROCYTES	LEUCOCYTES	NORMOBLASTS PER 100 WBC
1				
2	7.0	1,250,000	400,000	400
3				
4	14.0	4,250,000	40,000	85
5	16.0	4,900,000	11,000	8
6	17.0	5,100,000	11,500	5
7	17.0	5,190,000	10,000	3
8	15.4	5,300,000	10,000	3
9	14.5	4,800,000	9,500	2
10				
11	12.5	4,050,000	8,600	1
12	12.0	3,700,000	8,600	1
13	12.5	4,250,000	8,000	0
14	13.0	4,250,000	10,950	0
15				
16	12.5	4,220,000	11,000	0
17				
18	11.5	3,850,000	14,500	0
19				
20	10.5	3,660,000	16,000	0
21	10.5	3,680,000	16,400	0
22	10.8	3,770,000	10,550	1
23	9.3	2,890,000	15,500	1
24				
25	9.4	3,190,000	23,500	1

TABLE II. HEMATOLOGICAL COURSE OF INFANT "M. K."

DAY OF LIFE	HEMOGLOBIN IN GRAMS	ERYTHROCYTES	LEUCOCYTES	NORMOBLASTS PER 100 WBC
1				
2				
3	16.0	3,660,000	49,000	82
4	17.2	5,030,000	35,000	62
5	18.0	4,700,000	50,000	200
6	17.0	3,500,000	20,000	65
7	15.0	4,050,000	20,000	40
8	14.0	4,000,000	18,000	15
9	14.0	4,250,000	17,000	8
10				
11				
12	13.0	4,100,000	18,000	3
13				
14	16.0	4,110,000	17,000	1
15				
16				
17				
18				
19	9.5	3,100,000	12,000	0

## SUMMARY

Two cases of erythroblastosis fetalis complicated by severe generalized edema successfully treated with concentrated human serum albumin are reported. The first was one of twins, in which the untreated sibling died. In the second case, blood studies were done and it was found that the use of the serum albumin corrected an early fall in the blood protein level with subsequent elimination of the severe generalized edema.

It is postulated that liver damage, frequently a feature in severe erythroblastosis fetalis, with a disturbed blood protein level was the causative mechanism of the edema, and that the serum albumin restored the level. Studies are now in progress further to elucidate these factors.

## REFERENCES

1. Halperin, J., Jacobi, M., and Dubin, A.: *Am. J. Obst. & Gynec.* 50: 326, 1945.
2. Wiener, A. S., Wexler, I. B., and Gamrin, E.: *Am. J. Dis. Child.* 68: 317, 1944.
3. Leonard, M. F.: *J. PEDIAT.* 27: 249, 1945.

# DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY

## VI. ACUTE ILIAC LYMPHADENITIS

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WHEN acute inflammation of superficial lymph nodes occurs, accurate diagnosis can usually be readily established. When, however, the deeper lymph nodes are involved, diagnosis becomes more difficult, and a number of other important conditions must be considered.

The deep iliac lymph nodes are situated retroperitoneally, deep in the iliac fossae, lying adjacent to the external and common iliac vessels and anterior to the psoas muscles. Their afferent lymphatics drain the inguinal and sub-inguinal glands, the deep lymphatics of the abdominal wall, the adductor region of the thigh, the glans penis, urethra, prostate, fundus of the bladder, cervix uteri, and upper vagina. In the St. Louis Children's Hospital, the diagnosis of acute inflammation of the deep iliac lymph nodes has been made in eleven patients with confirmation by operation in six. An analysis of our cases follows.

The ages of the patients varied from 22 months to 12 years. There was an almost equal distribution between sexes, six males and five females. Most of the cases reported in the literature have likewise occurred in children, with also a nearly equal distribution between males and females.<sup>4, 7, 8</sup>

Upper respiratory infections immediately preceded the onset of illness in two instances, trauma to the lower abdomen and urinary tract infection each in two cases, palmar abscess with concomitant vaginitis once, and in four cases no definite history of any preceding infection or trauma could be elicited.

In the literature<sup>2, 3, 4, 7, 9</sup> the predisposing factors mentioned have been appendicitis; hematogenous spread from upper respiratory infection, impetigo, furunculosis, and pneumonia; trauma; intestinal diverticulitis; infection of lower extremities; perforating intestinal foreign body; gastroenteritis; miscarriage; puerperal infection following delivery; and infection in the posterior urethra, prostate, or rectum.

Fever was a constant finding in the reported cases. It was usually very high in cases with an acute onset, but low in cases developing more gradually. In ten of our cases, fever was noted before admission, varying in duration from one to thirty days. During the period of hospitalization, all the patients had fever, usually of a septic type with peaks from 38.6 to 41.6° C. Temperatures above 38° C. have persisted as long as sixty days.

Abdominal pain and/or pain in the hip region or thigh were present in all except one patient\* for several days before the patient was first seen. Four

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\*Signs of iliac adenitis developed in this patient only after the second hospital day.

patients complained of abdominal discomfort, which varied from a dull ache to a severe, intermittent, sharp, stabbing pain. In one case the abdominal pain was generalized for three days, with final localization in the right lower quadrant. The remaining seven patients had pain in the hip, thigh, or lower lumbar regions.

Constant or intermittent abdominal pain was also usually noted in the reported cases,<sup>3, 4, 5, 7, 8, 9</sup> and as in our experience, pain was also frequently noted in the hip region or occasionally referred down the thigh to the knee.<sup>8</sup>

Two of our patients had dysuria, one also presenting frequency. In none of our patients was any evidence of urinary tract infection found. Dysuria, pain at the end of micturition, and even reflex urinary retention have been reported by Coutts<sup>3</sup> who demonstrated transient hydronephrosis together with a temporary increase in blood urea due to ureteral compression by the enlarged glands. With cystoscopy in several cases he noted bulging of the bladder wall with a bullous edema nearest the site of the inflamed gland.

Nausea and vomiting were not prominent symptoms in our cases, reflecting the very slight degree of peritoneal irritation usually present. This was also true in the reported cases, a point of considerable importance in excluding acute appendicitis.

Psoas spasm was noted in eight of our eleven patients and was also one of the most characteristic findings in the reported ones.<sup>5, 7, 9</sup> The muscle spasm was always quite marked, so that the patient either could not walk at all or walked with a decided limp. Extension of the affected leg was always impossible, and the patients invariably preferred to lie in bed with the thigh adducted and flexed on the abdomen at all times. In contrast, however, there was no limitation of motion except for extension of the thigh. This point is extremely important in eliminating the diagnosis of hip joint disease.

Abdominal tenderness and rectus muscle spasm were present in ten of the eleven cases. The former varied slightly and was sometimes generalized but occasionally marked and localized over the lower abdomen and accompanied by marked muscle spasm. In five cases, palpable masses were present in either the right or left lower quadrants just above Poupart's ligament. These were very tender and firm. In the reported cases, abdominal masses had also usually been found.<sup>4, 6, 7</sup> It must be emphasized that the early cases will not have a palpable mass since this develops gradually as the glands enlarge or suppurate and, therefore, is to be expected only in the more chronic cases. Ladd and Gross<sup>9</sup> noted that approximately one-half of their cases went on to suppuration with abscess formation.

Occasionally the enlarged glands or abscesses have been palpated on rectal examination, although this was not true in any of our cases.

In every case there was a leukocytosis varying from 10,750 to 35,250 with a moderate shift to the left in the differential. Anemia was reported in cases of long standing.

Blood culture was positive for hemolytic *Staphylococcus aureus* in two of our cases and sterile in five others. Culture from iliac nodes or abscesses showed *Staph. aureus* in three cases and hemolytic streptococcus once.

Of the reported cases the most common organism isolated from blood, infected glands, or abscesses has been hemolytic *Staph. aureus* with the hemolytic streptococcus next in frequency.<sup>1, 2, 4, 6, 7, 8</sup> The pneumococcus has also been isolated,<sup>7</sup> and Coutts,<sup>3</sup> and Hyman<sup>4</sup> feel that *Bacillus coli* is occasionally responsible.

Operation was performed in six cases. Enlarged, chronically infected iliac glands without abscess were found twice. Extraperitoneal abscesses were found in five cases, once at a second operation when at first only enlarged lymph nodes were noted. Four of the abscesses were located in the iliac fossa, and the fifth was in the lower lateral abdominal wall with a tract leading downward into the iliac fossa. All six of the patients operated upon eventually recovered. Tuberculin tests were uniformly negative. Roentgenographic examinations of the bones of the pelvis, hip joint, and femur in seven of our patients revealed no bony changes. The other four patients were not examined by x-ray.

Three of our cases were treated conservatively without specific therapy. General supportive measures were used with *drainage of the abscess as soon as definite localization occurred*. Use of sulfonamide drugs alone in six instances failed to produce prompt clinical improvement. In the last two patients treated here, penicillin was used with very prompt subsidence of signs and symptoms. In both instances a hemolytic *Staph. aureus* bacteriemia was found to be present.

#### SUMMARY OF TWO REPRESENTATIVE CASES

CASE 1.—I. G. A., an 8-year-old girl, had four chills three weeks before admission and continued to run a low-grade fever daily after that date. Malaise and weight loss were noted, and for one week a limp of the right leg, and pain in the right hip were present. Physical examination revealed a chronically ill girl, temperature, 38.6° C. There was a firm tender mass about the size of an egg just above Poupart's ligament in the right lower quadrant. The right thigh was held adducted and flexed on the abdomen. Attempted extension of the right leg and thigh caused severe pain. Laboratory findings: white blood cells, 18,200 with a moderate shift to the left; hemoglobin, 85 per cent; red blood cells, 3.5 million; urine negative; tuberculin negative. X-rays of both hips and pelvis showed no bone changes. No specific therapy was given; the temperature remained elevated, and the white blood count rose to 31,600. On the seventh day, a laparotomy was performed, revealing enlarged retroperitoneal iliac nodes which on examination showed evidence of chronic infection. Following operation, the temperature reached 39.6° C. with wide daily fluctuations. Abdominal pain, tenderness, and right psoas spasm persisted. On the fifteenth postoperative day the wound broke open, evacuating a large amount of pus which on culture revealed hemolytic streptococci. The temperature then rapidly dropped to normal, and the patient was discharged on the thirty-third day.

CASE 2.—R. E. B., 7-year-old white boy, entered the hospital, complaining of fever, malaise, and sharp pains in the left thigh of four days' duration. Before admission the pain shifted to the left hip and flank, and nausea and vomiting developed. For three days before admission there was dysuria and frequency. Physical examination: Temperature, 38.8° C. The patient was acutely ill with marked tenderness in the left lower quadrant and left inguinal region. The left thigh was rigidly flexed on the abdomen and could not be extended. The left hip joint could easily be moved through all its motions without pain, except for extension which caused severe pain. Laboratory findings: white blood cells, 16,750 with a moderate shift to the left; urine negative; blood culture, hemolytic *Staph. aureus*. X-rays of hip joints and femurs showed no bone changes. Tuberculin negative. He was placed on penicillin 10,000 units subcutaneously every two hours and

sulfadiazine. Sulfadiazine was discontinued on the fourth day, after the staphylococcus was reported present in the initial blood culture. There was a rapid improvement of both signs and symptoms; the temperature dropped to normal on the fourth day, and the patient was discharged on the tenth day much improved.

#### DISCUSSION

The syndrome of iliac lymphadenitis usually presents a fairly definite picture. There may be a history of preceding infection or trauma with either an acute onset or one which is slowly progressive. Fever is always present. Pain is present either in the lower abdomen, thigh, hip region, or knee on the affected side. Usually there is psoas spasm with limping and flexion of the thigh on the abdomen. Tenderness and muscle spasm are usually present in the lower abdomen on the affected side. A mass may be present in the lower abdomen, especially in long-standing cases which may also show weight loss and anemia. Of particular importance is the fact that the hip joint on the affected side can be moved through all its motions, except extension, without pain. Occasionally urinary symptoms of dysuria and frequency may be noted. Signs of peritoneal irritation, namely nausea and vomiting, are usually absent.

Several conditions must be considered in the differential diagnosis.

*Osteomyelitis* of the femur or bones of the pelvis must be ruled out. Although pain in the thigh is a frequent complaint, tenderness on deep palpation of the femur and the palpable bones of the pelvis is absent. Localizing signs of redness, swelling, or increased heat over any portion of the thigh or hip are absent. Roentgenographic examination of the bones of the pelvis and thigh at no time reveals bone changes. Pyogenic osteomyelitis of the bodies of the lower lumbar vertebrae with direct extension of the infection into the psoas muscle may give signs and symptoms indistinguishable from those found in iliac adenitis. The differential diagnosis then may only be made when areas of destruction in the vertebrae are found by x-ray examination.

*Infection in the hip joint* can usually be ruled out by demonstrating free and painless motion of the joint. The only limitation of motion is that due to psoas muscle spasm with the thigh kept flexed on the abdomen in the position of adduction. Attempted extension is very painful, and the leg and thigh cannot be completely straightened. Roentgenographic examination shows no evidence of change in the hip joint.

*Rheumatic fever* may be differentiated occasionally by the history alone. The history of migrating polyarthritides is lacking, and the joints are never red and swollen. Rheumatic nodules and evidence of acute rheumatic carditis are lacking. The abdominal mass is not present, nor do patients with rheumatic fever adopt a postural attitude with persistent flexion of the thigh such as is seen with psoas spasm in iliac lymphadenitis.

*Appendicitis* may be hard to rule out if the involvement is on the right side. In iliac lymphadenitis signs of peritoneal irritation, nausea, and vomiting are usually absent, and examination reveals no rebound tenderness. The localized point of maximal abdominal tenderness is just above Poupart's ligament and below McBurney's point. Psoas spasm is usually more persistent and more

marked than that sometimes found in acute appendicitis. The temperature is frequently higher than one would expect to find with an early acute appendicitis. Occasionally iliac lymphadenitis is accompanied by enlargement and signs of infection in the corresponding inguinal and/or femoral glands. The initial complaint with acute appendicitis is usually abdominal pain, but with iliac lymphadenitis the initial pain is usually in the hip, thigh, or knee.

*Psoas abscess of tuberculous origin* is occasionally seen. Here, too, the typical picture of psoas spasm is seen, but in addition one finds physical and roentgenographic evidence of disease of the vertebral column and frequently of the lungs also. The tuberculin test is positive, and the onset of this disease is much slower and more insidious.

*Recommended Treatment.*—The plan of treatment should vary somewhat depending on whether or not an abscess is present. The early acute cases are seen when there is no suppuration of the iliac nodes. As *Staph. aureus* is the most common causative organism, we feel the drug of choice is penicillin given subcutaneously every two hours. For the average child, from 10,000 to 20,000 units at each injection should be sufficient. Since some cases might be due to *B. coli*<sup>3</sup> or other penicillin-resistant organisms, a sulfonamide should be given concomitantly in appropriate dosage. In all of the cases which we have treated with such a regime there was rapid and complete recovery without abscess formation.

The cases in which an abscess is present are usually those which have had a gradual onset. The symptoms have usually persisted for several weeks, and a mass has almost always been present in the lower abdomen when the patient was first seen. These patients should receive penicillin and sulfadiazine as outlined previously. In addition, however, surgical drainage of the abscess must be carried out after localization has occurred. This operation as described by Neuhof and Arnheim,<sup>8</sup> and Ladd and Gross<sup>9</sup> is not difficult or unduly dangerous when a careful extraperitoneal approach is used. They had no operative deaths in their cases, although the average operative mortality reported in the literature is approximately 5 per cent.<sup>8</sup>

#### CONCLUSIONS

1. Iliac lymphadenitis is a not infrequent condition during childhood and must be differentiated from rheumatic fever, osteomyelitis, suppurative arthritis, appendicitis with or without abscess formation, and tuberculosis of the spine with psoas abscess.
2. The causative organism is usually the hemolytic *Staph. aureus*, although hemolytic streptococci and pneumococci have also been identified, and *B. coli* justifiably suspected.
3. The most characteristic features of the condition are fever and leucocytosis, pain in the abdomen, hip, thigh or knee, psoas spasm with protective flexion of the thigh on the abdomen, free motion of the hip joint except for extension of the thigh, and sometimes lower abdominal tenderness with a mass just above Poupart's ligament.



4. Early vigorous treatment with penicillin and sulfonamides may prevent abscess formation. In cases with an abscess present, extraperitoneal surgical drainage must also be employed.

## REFERENCES

1. Hamann, C. A.: Cleveland M. J. 6: 399, 1907.
2. Huggins, R. H.: Surg., Gynec. & Obst. 12: 276, 1911.
3. Coutts, W. E.: Ann. Surg. 86: 782, 1927.
4. Hyman, A.: Ann. Surg. 91: 718, 1930.
5. Bailey, H.: Practitioner 124: 223, 1930.
6. Frank, L.: Ann. Surg. 105: 975, 1937.
7. Irwin, F. G.: Arch. Surg. 36: 561, 1938.
8. Neuhoof, H., and Arnheim, E. E.: Ann. Surg. 119: 741, 1944.
9. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1941, W. B. Saunders and Company.

## THE TREATMENT OF SCABIES IN CHILDREN WITH A NEW SARCOPTICIDE

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THAT the incidence of scabies rises sharply during wartime is well appreciated. Scabies reached epidemic proportions in England during World War II and is apparently on the increase in the United States.<sup>1</sup> It is generally maintained that inadequate housing facilities, necessitating the overcrowding of living quarters, is an important factor in the spread of this parasitic skin infestation. One may therefore expect it to become even more widespread in our own country until the housing situation is bettered.

Of all the many sarcopticides recommended and used throughout medical history, not one has proved entirely satisfactory.<sup>2</sup> Sulfur preparations have undoubtedly enjoyed the widest usage. Although sulfur preparations have in general been satisfactory, they have had a number of disadvantages, such as objectionable odor and messiness, high percentage of untoward skin reactions, and necessity of efficient washing and scrubbing of the patient before treatment.

Recently the use of benzyl benzoate against the *Sarcoptes* has become popular in the United States. The benzyl benzoate treatment is by no means new, as this drug is the main active ingredient of balsam of Peru, which has been used for many years.<sup>3</sup> Apparently Sachs and Juliusberg<sup>4</sup> in 1900, first advocated benzoate itself as a sarcopticide; however, it was not until 1937, that Kissmeyer<sup>5</sup> popularized the medicament. During the recent war this drug was widely used in the epidemic in Great Britain; and British dermatologists now seem to believe that it is superior to sulfur in deadliness and speed of action against the itch mite.

Apparently benzyl benzoate may not be used indiscriminately. Intractable scrotal dermatitis has been known to occur after its use,<sup>6</sup> and Daughtry<sup>2</sup> has recently described several cases of severe skin reactions attributable to it. Furthermore, benzyl benzoate is not well-suited to therapy in infants and small children, as its application always causes a certain amount of stinging, and when applied to raw areas may be extremely painful.<sup>6</sup> In his own practice the writer has hitherto tended toward the use of sulfur formulas in the treatment of scabies, but has never prescribed the vigorous washing and scrubbing of small children.

Recently the writer has had the opportunity to treat twenty-two cases with a new sarcopticide, an ointment containing Zyclophen.\* The results to date, it is felt, warrant bringing this new formula to the attention of pediatricians. This

\*Zyclophen is the name given by the U. S. Standard Products Company of Woodworth, Wis., to a mixture of equal parts by weight of 4-chloro-3, 5-dimethylphenyl hydrogen di-camphorate and *ortho*-phenylphenol.

ointment is an invention of Dr. Max N. Huffman of the Southwestern Medical Foundation, and it is composed of the following ingredients:

4-Chloro-3,5-dimethylphenyl hydrogen <i>dl</i> -camphorate	1.0 Gm.
<i>ortho</i> -Phenylphenol	1.0 Gm.
Anhydrous lanolin	4.0 Gm.
White petrolatum	94.0 Gm.

A one-half ounce jar of this ointment was given to the parents of the infected child with the instruction to use only on affected parts twice daily (morning and night) for two successive days. No directions were given for unusual or extra bathing of the patient.

#### CASE REPORTS

CASE 1.—C. F., a girl, 6 years of age, had a scabietic infection of 4 months' duration. She had previously been under the care of a physician who had used a sulfur-foam preparation without benefit. When first seen her condition was that of typical scabies with secondary involvement. In addition to pustules on the hands and about the body, she had the typical ring around the waist. Her parents spoke of her not being able to sleep because of intense itching. She cleared completely after the two-day treatment with zyclophen ointment.

CASE 2.—L. F., 6 years old, was the daughter of a war worker who had been engaged in war work in St. Louis, Dallas, New Orleans, and Houston. The child had been under treatment for scabies in each city but the infection had recurred each time. In Austin she presented typical scabies with rather considerable secondary involvement. Treatment as described resulted in complete cure. There has been no recurrence within two months.

CASES 3 AND 4.—Two boys, B. P. and J. P., presented similar pictures. They had each been treated with a sulfur-foam preparation but had each suffered a further outbreak of *Sarcoptes* activity. With these boys zyclophen was highly effective.

CASES 5 TO 22.—These eighteen cases represented an outbreak of scabies in one of the local schools. The group was about evenly divided according to sex and presented no unusual features. Each child was given the two-day treatment. Cure was complete in every case as evidenced by subsequent examination.

#### COMMENT

All twenty-two patients, as is shown in the case reports, were cured after four applications of the ointment.

The writer definitely prefers zyclophen to any preparation he has used for the treatment of scabies in children. Management with it has been simplicity itself, and no skin reactions have been observed as yet. It is obvious, however, that not nearly enough cases have been treated to justify any statement regarding the sensitizing properties of the drug. The ointment has no odor and does not stain clothing; its application, so far, has not been painful to any child.

In one particular, zyclophen is markedly superior to the usual medicament employed against the itch mite, and that is in respect to its effectiveness in clearing up the secondary pustular involvement so often seen in scabies of long standing. This property is no doubt attributable to the fact that the drug is not only a sarcopticide but a bactericide and fungicide as well.

It is interesting to note that the percentage of active ingredient in the usual sarcopticide is relatively high. Thus, sulfur is ordinarily administered in 10

to 18 per cent strength, and benzyl benzoate in 20 to 25 per cent concentration. This item is of considerable importance, particularly in children, since the entire body (except for head and neck) is commonly covered with the preparation. In contrast, the concentration of active material in the zyclophen ointment was only 2 per cent;\* this is surely to be regarded as a step in the right direction if it can be conclusively shown that this 2 per cent of drug is no more toxic nor irritative than a like concentration of one of the other parasitocides.

#### SUMMARY

A series of twenty-two cases of scabies in children has been treated with a new parasiticide, zyclophen. Cure in each case has been rapid, complete, non-painful, and free from untoward reactions.

#### REFERENCES

1. Oppenheim, M., and Smith, H. A.: *Arch. Dermat. & Syph.* 48: 370, 1943.
2. Daughtry, DeW. C.: *J. A. M. A.* 127: 88, 1945.
3. Mellanby, K., Johnson, C. G., and Bartley, W. C.: *Brit. M. J.* 2: 1, 1942.
4. Sachs, R.: *Deutsche med. Wchnschr.* 26: 631, 1900.
5. Kissmeyer, A.: *Lancet* 1: 21, 1937.
6. Leading Article: *Brit. M. J.* 2: 44, 1942.

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Dr. Huffman believes that the two active ingredients in zyclophen have a synergistic effect upon each other. (Personal communication.)

## STREPTOMYCIN IN PEDIATRICS

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SINCE the isolation of streptomycin by Waksman in 1943, a number of investigations on its in vitro and in vivo influence have suggested that this agent exerts its greatest antibacterial action against those organisms which have proved most resistant to penicillin, the gram-negative rods. The results are summarized in Table I. It is the aim of this report to analyze the published data and those of the authors in order to determine the value of in vitro sensitivity tests as an index of the therapeutic efficiency of streptomycin in infections caused by the organisms listed.

The in vitro sensitivities of a number of gram-negative rods expressed as MEC (minimal concentration of units per cubic centimeter of culture media necessary to prevent growth) are listed in two columns; in the first are those obtained from published reports and in the second are the values obtained at the Babies Hospital.

Analysis of the figures in column I suggests that this antibiotic will prove to be an effective therapeutic agent against infections caused by all of these organisms with the possible exception of about one-half of the infections caused by *Pseudomonas aeruginosa*. There are no published values for type b *Hemophilus influenzae*. Reports on a few strains of nontypable varieties indicate that these organisms are very sensitive to streptomycin. *Pasteurella tularensis* has exhibited a striking degree of sensitivity; the range of variation between strains has been narrow.

There are two values listed in column I for each of the group of four organisms which most frequently infect the urinary tract but which in young infants occasionally invade the blood and meninges. The first figure represents the MEC obtained for the majority of strains of each organism. The second figure shows that certain strains of three of the organisms of this group resist high concentrations; 50 per cent of the strains of pyocyanus show this trait but the percentage is smaller for other organisms. The wide variation among different strains in this whole group has been confirmed by a number of investigators.

The values listed for *Eberthella typhosa* and Brucella strains suggest that both organisms are susceptible to concentrations easily obtained in biologic fluids by the dosage schedule commonly used.

How do the in vitro sensitivities in column I correlate with therapeutic results in human infections? In tularemia the in vitro tests provide an accurate index of therapeutic effectiveness of streptomycin. The published ex-

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TABLE I. CORRELATION BETWEEN IN VITRO SENSITIVITY AND THERAPEUTIC VALUE

BACTERIAL AGENT	IN VITRO SENSITIVITY		THERAPEUTIC VALUE
	*MEC UNITS PER C.C.		
	PUBLISHED REPORTS	BABIES HOSPITAL	
	I	II	
<i>H. influenzae</i>		0.8 - 10.8	+
<i>P. tularensis</i> (Tularemia)	0.15 - 3		+
<i>E. coli</i>	< 8 - > 256	13.3 - 25	+
<i>A. aerogenes</i>	< 8 - > 256	5	+
<i>Proteus</i>	< 8 - > 28	15 - 100	+
<i>Ps. aeruginosa</i> (Pyocyanus)	< 40 - > 256	100 - 200	±
<i>E. typhosa</i>	6 - 18	25 - 75	?
<i>Brucella</i>	0.1 - 0.5		?
<i>S. paratyphenteriae</i>	1.4 - 7.5	25	N.D.†
<i>Salmonella</i>	3 - 28	25 - 200	N.D.†
<i>K. pneumoniae</i> (Friedlanders)	0.15 - 2.5	1.6	N.D.†
<i>H. pertussis</i>		3 - 5	N.D.†

\*MEC—Minimal effective concentration.

†N.D.—Not determined.

perience with streptomycin therapy in tularemia is limited to seven patients but the results were so striking, in degree and rapidity of improvement as well as in consistency of response, that one is led to believe that streptomycin will prove to be the most efficacious form of treatment yet applied to this disease.

Infections of the urinary tract constitute the largest group of infections in which the therapeutic value of streptomycin has been investigated. Most of these patients were members in the Armed Forces and developed urinary tract infections following injury to the spinal cord. The results in this group have not yet been published. However, verbal reports justify the conclusion that streptomycin represents an important contribution to therapy of urinary tract infections. On the other hand, the appearance of resistant strains during treatment has proved to be a significant problem. The civilian published experience is quite limited but is in agreement with this view. Herrelle has reported the largest series. Striking clinical improvement of the patients is reported but persistence or recurrence of infection and the emergence of resistance of the organisms have occurred fairly frequently. Nonetheless, the statement of Helmholtz that streptomycin is the most effective single agent for treating mixed infections of the urinary tract may prove to be true. The limitations should emphasize the need to administer large doses from the beginning of treatment and the advisability of avoiding a large intake of fluid which will result in diluted urine. Under the schedule of administration to be described, the concentration of streptomycin in the urine has been maintained regularly above 250 units per cubic centimeter and at times reaches 1000 units per cubic centimeter when the fluid intake is normal and the kidney function is good.

In typhoid fever and brucellosis the results of treatment with streptomycin have been very disappointing. Only about a dozen patients with

typhoid fever and six with brucellosis have been reported but it seems clear already that little can be expected from streptomycin in these diseases. From the published figures there is no correlation between the in vitro influence and the therapeutic value.

It must be emphasized that the MEC values taken from published data have been obtained by in vitro tests carried out under widely varying conditions so they cannot be used as a basis for comparing the in vitro sensitivities of these different varieties of organisms.

*Relation Between In Vitro Influence and Therapeutic Effect of Streptomycin in H. influenzae Meningitis.*—The influence of a number of variables was studied in an effort to standardize an in vitro test which might serve as an index of sensitivity range of a representative number of *H. influenzae* strains and also as a guide to therapeutic effectiveness of streptomycin in an individual patient with meningitis. Three principles were applied. The inoculum was large (3 to 1,700 million organisms), the medium was optimal (Levinthal broth and agar), and the incubation period adopted for the test was 48 hours. Cultures of *H. influenzae* in Levinthal broth and Levinthal agar after a 6-hour incubation period were compared as sources of organisms for the test. A 2 mm. platinum loopful from each of these sources was seeded on each of a series of Levinthal agar plates containing varying concentrations of streptomycin ranging from 0.5 to 10.8 units per cubic centimeter. After incubation for 48 hours the lowest concentration of streptomycin which completely inhibited growth was defined as the minimal effective concentration or MEC of the strain. Fifty strains of type b *H. influenzae* have been studied by this method; all were found to be completely inhibited by concentrations between 0.8 and 10.8 units per cubic centimeter. Only three of these strains resisted concentrations beyond 7.5 units per cubic centimeter. A few cultures of types a, c, d, e, and f *H. influenzae*, as well as several strains of nontypable *H. influenzae*, have exhibited a comparable degree of sensitivity. Twenty-five of the type b strains were isolated from patients with influenzal meningitis prior to their streptomycin treatment; their range of sensitivity was between 0.8 and 7.5 units per cubic centimeter.

The strains isolated from two patients after the start of streptomycin treatment exhibited capacity to thrive in the presence of streptomycin in a concentration of 1,000 units per cubic centimeter. All of the sixteen sensitive strains studied exhibited increased resistance to streptomycin after a few subcultures in media containing streptomycin. Most of them grew in the presence of 525 units per cubic centimeter within a period of two weeks. Thus we were provided with a group of strains which were resistant to high concentrations of the antibiotic according to in vitro tests. Mouse protection tests were carried out to compare the in vivo sensitivity of the two groups: those showing sensitivity and those exhibiting resistance in vitro. The smallest single dose of streptomycin per mouse, which was sufficient to protect 50 per cent of the mice receiving 20,000,000 organisms each, or 1 million MLD (minimal lethal dose), was determined for both the sensitive and resistant

strains. A high degree of correlation was demonstrated between the MEC in vitro and the MED or minimal effective dose in mice.

Despite the agreement between the in vitro and in vivo tests neither method enabled us to select in advance the patients whose strains became resistant after the beginning of streptomycin treatment. Our therapeutic results suggest that it is the severity of infection and presumably the size of the bacterial population which determine whether the strain from a given patient will become resistant. This experience confirms the view held by most authorities in this field; any sensitive strain, if the population is large enough, contains a very small fraction of organisms which possess initially the capacity to thrive in the presence of any of its effective antibacterial agents (sulfonamides, penicillin, gramicidin). The apparent development of resistance appears to represent a selective process which eliminates the sensitive organisms and therefore permits the emergence of resistant members.

While these procedures fail to detect traits of resistance in the original strains, their use in determining the sensitivity of organisms cultivated from patients after the start of streptomycin treatment has provided a clear indication of the effectiveness of this antibiotic in the patients from whom the strains were isolated. In the group of patients in whom streptomycin treatment proved successful all strains isolated from spinal fluid or respiratory tract after the beginning of the treatment were shown to be sensitive. On the other hand, treatment was unsuccessful in two patients whose strains exhibited marked resistance during streptomycin administration. In one of these the organism isolated from the nasopharynx proved to be just as resistant as the strain grown from the spinal fluid.

The results of treatment of the twenty-five patients with type b *H. influenzae* meningitis who received streptomycin alone or in conjunction with other agents are summarized in Table II. Each patient is classified according to the severity of his infection and the therapeutic agent or agents used. Severity of infection was judged by two standards, clinical signs and the concentration of sugar in the original spinal fluid. In the cases of mild or average severity the level was above 30 mg. per cent in all but one patient whose

TABLE II. SUMMARY OF TREATMENT OF 25 PATIENTS WITH TYPE B *H. INFLUENZAE* MENINGITIS

NUMBER PATIENTS TREATED	SEVERITY OF INFECTION	S.M. ALONE			SERUM AFTER 4 DAYS OF S.M.			S.M. AFTER UNSUCCESSFUL SERUM AND SULFADIAZINE			S.M. SERUM AND SULFADIAZINE INITIALLY		
		R	S	D	R	S	D	R	S	D	R	S	D
13	Mild-average	12						1					
8	Severe chronic		2			2		1	1	1	1		
4	Severe early				1						3		
TOTAL						R	S	D					
						19	3	3					

S.M., streptomycin.

R, recovered.

S, survived.

D, died.



value was 24. In the severe group, whether the infection was in chronic or early stage, the concentration of sugar in the spinal fluid before treatment with streptomycin was 15 mg. per cent or below. The patients are divided into four groups according to the therapy received: streptomycin alone; streptomycin alone for four days after which time type-specific antiserum and sulfadiazine were added; streptomycin after unsuccessful treatment with type-specific antiserum and sulfadiazine; and those treated with all three agents initially. The results of treatment are recorded under *R* for complete recovery, *S* for those who survived but who exhibited serious cerebral injury, and *D* for those who died. All of these twenty-five patients, with one exception, had received sulfadiazine at home or in other hospitals before institution of streptomycin therapy. It can be seen that when the infection is of mild or average severity streptomycin alone brings about complete recovery. While, on the whole, clinical improvement was less rapid than that seen following serum treatment, the changes in the spinal fluid indicating clearing of infection appeared just as promptly as those seen following serum therapy. In nine of the twelve patients who recovered, the spinal fluid cultures proved sterile 24 hours after initiation of streptomycin therapy; in the other three, after 48 hours. The return to normal of the chemical constituents of the spinal fluid was equally rapid. When the disease is severe and other therapeutic agents are not used to supplement streptomycin until after four days or longer the results are very disappointing. In two of the five patients with severe forms of the disease, treated with streptomycin alone for four days or longer, the failure of the antibiotic to eradicate the infection was due to emergence of resistance of the infecting strains. The strains isolated from the spinal fluid after start of streptomycin exhibited the capacity to grow in the presence of 1,000 units per cubic centimeter. In the group of patients with severe infections, the disappointing results of treatment with the two forms of therapy, used separately have led us to adopt the policy of administering all three agents initially: streptomycin, type-specific antiserum, and sulfadiazine. Four patients with severe infections have been treated according to this plan and appear to have recovered completely.

Thus it is seen that the results of in vitro sensitivity tests do provide an index of therapeutic effectiveness of streptomycin in influenzal meningitis.

*Application to Other Gram-Negative Rods of Methods Used to Study in Vitro Sensitivity of H. influenzae.*—The in vitro method used for testing *H. influenzae* sensitivity was applied to a number of other gram-negative organisms. The results are listed in the second column of in vitro sensitivity in Table I. All strains were either recently isolated or had been preserved by drying and sealing under vacuum shortly after cultivation from patients. It is of interest that with the exception of *Escherichia coli*, *Klebsiella pneumoniae*, *Aerobacter aerogenes* (organisms against which sulfonamides are effective) and *Hemophilus pertussis*, the MEC and the range of sensitivities are significantly greater than those found for *H. influenzae*. Only a much greater clinical experience with streptomycin therapy in these infections can determine whether

the *in vitro* test, which has provided a good index of therapeutic effectiveness of streptomycin in influenzal meningitis, will also serve as an indication of its value in other infections. At least it permits an *in vitro* comparison of the influence of this agent on many gram-negative organisms. From the clinical data available the results of the *in vitro* method described are in better agreement than those obtained by methods already published. The growth of very few colonies in the higher concentrations, thus resulting in a high MEC, is in line with the frequency of recrudescence of infection, and demonstration of resistance of surviving strains.

*Schedule of Therapy Used in Patients With Influenzal Meningitis.*—The twenty-five patients presented were treated according to the following schedule: an amount of streptomycin solution containing 20,000 units per pound of body weight was introduced by the intramuscular route daily. This was given in eight doses at 3 hour intervals in a concentration of 50,000 units, or less, per cubic centimeter or by a continuous intramuscular drip in a total volume of 240 c.c. of physiologic saline. The drug was also administered intrathecally to all patients; the injections, usually one a day, varied in total number depending upon the response of the patient, and the dose was between 25,000 and 50,000 units depending upon the severity of the infection. Table III shows the variations in concentration of streptomycin in blood and spinal fluid in eleven patients.

On this dosage there were no toxic manifestations which persisted after withdrawal of the drug. The duration of treatment was only five days for most patients. This period appears to be adequate for all patients with meningitis. The occurrence of eighth nerve deafness in a significant number of pa-

TABLE III. CONCENTRATION OF STREPTOMYCIN IN BLOOD AND SPINAL FLUID IN INDIVIDUAL CASES OF H. INFLUENZAE MENINGITIS, CORRELATED WITH DOSE OF STREPTOMYCIN ADMINISTERED AND SUSCEPTIBILITY OF INFECTING ORGANISM

CASE	STREPTOMYCIN CONCENTRATIONS (UNITS PER C.C.)		STREPTOMYCIN DOSE AND ROUTE (UNITS × 1000 EVERY 24 HRS.)				MEC <sup>5</sup> UNITS PER C.C.
	BLOOD <sup>1</sup>	SPINAL FLUID <sup>2</sup>	IM <sup>3</sup>			IT <sup>4</sup>	
1.	8.9 - 30.6	9.1 - 20.4	C.D.	20	per lb.	50	2.7
2.	5.1 - 10.1	-- --	q3h	20	per lb.	25	2.6
3.	4.2 - 8.5	11.5 - 5.1	q3h	20	per lb.	25	4.9
4.	10.1 - 19.1	11.8 - 20.0	q3h	20	per lb.	25	1.6
5.	6.2 - 14.6	6.2 - 6.0	q3h	20	per lb.	50	2.8
6.	5.5 - 14.5	5.0 - 28.0	q3h	20	per lb.	25	2.8
7.	3.3 - 6.5	8.5	q3h	20	per lb.	25	4.4
8.	7.3 - 22.0	4.9 - 16.3	q3h	20	per lb.	30	7.5
10.	5.8 - 12.2	5.1 - 12.1	C.D.	20	per lb.	50	2.5
11.	9.3 - 10.5	9.3 - 9.6	q3h	20	per lb.	25	1.6
12.	7.5 - 9.8	11.1	q3h	20	per lb.	25	4.4

<sup>1</sup>Specimen collected daily at irregular intervals when intramuscular dose was given by continuous intramuscular drip (C.D.). When streptomycin was given every 3 hours (q3h) the blood was withdrawn 3 hours after the last dose.

<sup>2</sup>Spinal fluid concentrations represent those found 24 hours after intrathecal dose listed.

<sup>3</sup>IM, intramuscular.

<sup>4</sup>IT, intrathecal.

<sup>5</sup>MEC, minimal effective concentration of streptomycin necessary to completely prevent growth on Levinthal agar in 48 hours.

tients treated for periods longer than one week makes it a serious responsibility to determine and use the shortest period of treatment which is effective.

*Indications for the use of Streptomycin in Pediatrics.*—Analysis of the available facts justifies the following tentative statements. Streptomycin is indicated in the following infections:

A. Streptomycin alone

1. Any type of *H. influenzae* meningitis of mild or average severity
2. Tularemia
3. Infections of urinary tract, blood, or meninges with *Proteus* or *Pseudomonas* groups
4. Severe cases of typhoid fever and brucellosis
5. Urinary tract infections with colon and aerobacter groups after failure with sulfonamides

B. Streptomycin plus sulfadiazine

1. Infections of the blood or meninges with any member of the gram-negative rod group which originates from the intestinal tract
2. Severe *H. influenzae* meningitis of types other than b

C. Streptomycin, sulfadiazine, and rabbit antiserum

1. Severe type b *H. influenzae* meningitis

D. There is reason to believe that streptomycin will prove to be an effective agent against bacillary dysentery, some of the salmonella types, *K. pneumoniae*, and *H. pertussis* infections, but clinical trial is inadequate for evaluation.

SUMMARY

Analysis of the published data shows lack of agreement between in vitro sensitivities and the clinical response to streptomycin of a number of human infections. Employment of an in vitro method which applied certain principles—use of a large inoculum (3 to 1,700 million organisms), an optimal medium (Levinthal broth or agar), and incubation period of 48 hours—yields sensitivities which are in better agreement with the available therapeutic results. Such statements must be accepted as only tentative until adequate clinical experience makes a final appraisal possible. The method offers a basis for comparison of all gram-negative rods studied. The test has provided a reliable index of the therapeutic efficacy of streptomycin in influenzal meningitis in which clinical trial does permit certain conclusions. The narrow range of sensitivity of all strains of *H. influenzae* studied prior to exposure to streptomycin is in agreement with the prompt recovery of patients who have meningitis of mild or average severity. On the other hand, in the severe cases therapeutic results with streptomycin alone have been disappointing; in two of the five unsuccessful cases the failures were due to emergence of resistance of the strains.

It is already clear that the therapeutic efficacy of streptomycin against most varieties of susceptible severe infections will be significantly influenced by emergence of resistance of the organisms.

## SALMONELLA ANATUM INFECTION

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**S***SALMONELLA ANATUM* was first described by Rettger and Scoville<sup>1</sup> in 1920, having been isolated from diseased ducklings. Since that time, it has been found to be widely distributed among fowls and animals.<sup>2</sup> Its presence in the lymph glands of normal hogs has been reported by Hormaeche and Salsamendi,<sup>3</sup> and by Rubin, Scherago, and Weaver.<sup>4</sup> Cherry, Scherago and Weaver,<sup>5</sup> in a study of retail meat products, isolated *S. anatum* from hog liver. Varela<sup>6</sup> records the isolation of *S. anatum* from chickens, cattle, and hogs. It was in 1934, that Kauffmann and Silberstein<sup>7</sup> reported for the first time the occurrence of *S. anatum* in human infection. This observation has subsequently been confirmed by various investigators. Edwards and Bruner<sup>2</sup> in a study of 3,090 *Salmonella* cultures derived from various sources encountered *S. anatum* as a human invader twelve times as follows: fecal carriers, 4; feces in gastroenteritis, 7; and in blood culture once. Their observations cover the period of 1934 to 1941. Bornstein,<sup>8</sup> in his paper on the *Salmonella* problem, classifies 500 cases of salmonellosis from North America and Cuba during the period of 1939 to 1941. *S. anatum* occurred 13 times as follows: carriers, 3; gastroenteritis, 7; and no data, 3. After eliminating *S. paratyphi* A and *S. paratyphi* B from consideration, *S. anatum* constituted 3 per cent of the remaining types, a figure identical with its frequency of occurrence in both Connecticut and the Lexington *Salmonella* Center as tabulated by Bornstein. Previously Bornstein and associates<sup>9</sup> had encountered *S. anatum* twice. No details were given. Galton and associates,<sup>10, 11</sup> in Florida, encountered *S. anatum* in 13 instances during 1942 and 1943. Three were from cases, 9 from normal persons, and one with history unknown. Seligmann, Saphra, and Wassermann<sup>12</sup> record the isolation of 27 cultures of *S. anatum* from 26 outbreaks. Fourteen of these were from cases of gastroenteritis; one from a case of cholecystitis; one from a case of cerebrospinal meningitis; 8 from healthy carriers; and 3 without clinical data. Stools were positive in 26 instances and the spinal fluid was positive once. Two fatalities were reported. Rubenstein, Feemster, and Smith<sup>13</sup> list ten isolations of *S. anatum* in Massachusetts during the period 1937 to 1943 of which 7 were sporadic, and one subclinical, and 2 release cases. The presence of *S. anatum* in food handlers is reported by Stone.<sup>14</sup> Varela<sup>6</sup> reports the isolation of the organism from children and adults in Montevideo and Mexico. Kauffmann,<sup>15</sup> in a survey of *Salmonella* infections, mentions eleven outbreaks of *S. anatum* enteritis in Norway due to cheese. He tabulates a total of 34 strains from 28 persons with 3 deaths in the series. With the exception of Denmark, *S. anatum* infections in other European countries are not mentioned. On the other hand, Kauffmann notes that this species has been reported from Java a number of

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times. From this it would seem that *S. anatum* is probably world-wide in distribution.

This report covers eight cases of *S. anatum* infection. Three of the eight cases occurred in March, 1944. There was no evidence of enteritis and the finding of the organism was incidental.

The organism was recovered first from a 9-month-old Negro female who was admitted to the hospital on March 2, 1944, for treatment of empyema. A culture of the pleural fluid obtained on March 4, was positive for pneumococci. On March 16, a second culture of the pleural fluid yielded both pneumococci and *S. anatum*. A single stool specimen was negative on culture. The case terminated fatally on April 8, 1944.

On March 9, 1944, a 2-year-old white male was admitted acutely ill with bilateral pneumonia. Abdominal distention was marked during the first five days of the patient's stay in the hospital. A stool culture taken on the fourth day for exclusion of typhoid fever yielded *S. anatum*.

A 4-year-old white female was admitted to the hospital on March 21, 1944, with a provisional diagnosis of bronchopneumonia and arthritis of eight days' duration. At time of admission the child appeared to be acutely ill. Her rectal temperature was 104.8° F., the pulse rate was 120, and the respiratory rate was 50. Marked cyanosis was present. There was localized tenderness over the trochanter of the left femur. The patient was placed in an oxygen tent, and given sulfadiazine and general supportive treatment. Blood cultures taken on the third and seventh days showed staphylococci. A stool culture taken on the seventh day yielded *S. anatum*. No evidence of diarrhea was noted. Further study of the case established a diagnosis of osteomyelitis and the patient was discharged in an improved condition on March 25, 1944.

In two of the above cases *S. anatum* was present in the stool apart from any evidence of gastrointestinal disturbance. This at least suggests the possibility that the patients were carriers of the organism.

An institutional outbreak of enteritis due to *S. anatum* occurred in the isolation wards during February and March, 1945, following the introduction of an initial case from the obstetric nursery. After the appearance of the second case, a survey of all involved personnel was made to ascertain whether or not a fecal carrier was the source. Cultures of stool specimens obtained from the attendants were negative for intestinal pathogens. Manual transfer of the organism from the initial case during routine care appeared to be the probable mode of transmission.

The case reports present clinical pictures of enteritis of a mild nature characterized by an abrupt onset, liquid green stools containing blood and mucus, and a relatively short duration. Prompt attention to the condition may have been responsible for the relatively mild nature of the disease.

CASE 1.—D. F., a newborn white female, was delivered spontaneously in the hospital on Feb. 17, 1945. She weighed 7 pounds, 2 ounces at birth. The infant was admitted to the nursery in apparently good condition and was started on breast feedings. On February 19, she weighed 6 pounds, 11 ounces. At this time she expelled several yellowish green stools that contained mucus. The rectal temperature was 98.8° F. On the following day five stools

were noted during an 8-hour period. The stools were liquid, green, and contained blood and mucus. The rectal temperature was 99.2° F. Oral feedings were discontinued and the infant was given 2½ per cent glucose in Hartmann's solution subcutaneously, one-half dram of kaopectate three times a day, and sulfadiazine orally. Bacteriologic examination of the stool revealed *S. anatum*. On the third day the diarrhea had subsided. One liquid green stool was noted. The rectal temperature was normal. The sulfadiazine, kaopectate, and parenteral fluids were continued and the infant was started on boiled skimmed milk and given water ad lib. No change in the treatment was made on the fourth day. The infant was greatly improved and spent a quiet night. The maximum rectal temperature was 99.6° F. On the fifth day the rectal temperature was normal. Parenteral administration of fluids was discontinued. The infant spent a quiet night and appeared to have recovered on the following morning. During the next 48 hours the temperature and bowel movements were normal.

CASE 2.—A. K. P., a 21-month-old white female child, was admitted to the hospital for treatment of tracheobronchitis, duration five days. On admission the child had a rectal temperature of 100.2° F., a respiratory rate of 30 per minute, and a pulse rate of 140 per minute. Stridor was present. The pharynx was inflamed but no membrane was noted. Smears and cultures of nose and throat were negative for diphtheria. The hemogram revealed no abnormality. Therapy consisted of steam inhalation, sulfadiazine, and general supportive treatment. The temperature varied from 99° to 103.8° F. during the first two days, but returned to normal the third day. Respiratory stridor disappeared about this time. On the fourth day the temperature ranged from 101.8° to 102° F. The child expelled three yellow liquid stools during an 8-hour period. Since it was believed that the respiratory infection was responsible, the patient was given 10,000 units of penicillin intramuscularly every three hours for a total dosage of 50,000 units. The next day the patient refused food. The temperature varied from 100° to 102° F. Three liquid stools containing a small amount of blood and mucus were noted. Culture of the stool yielded *S. anatum*. Oral feedings were discontinued for 24 hours and 5 per cent glucose in normal saline was given subcutaneously. The sulfadiazine was discontinued and the temperature ranged from 102° to 105.4° F. One soft stool was noted during 24 hours. On March 3, the child appeared to have recovered and rested quietly. She accepted liquid feedings and had no diarrhea. The rectal temperature was 99° to 99.4° F. A soft diet was given thereafter and the remainder of the hospital stay was uneventful.

CASE 3.—W. D. H., a 5-month-old white male, was admitted to the hospital on Feb. 24, 1945, for treatment of bilateral conjunctivitis and upper respiratory infection of one week's duration. At the time of admission the rectal temperature was 100° F. The respiratory rate was 20 per minute and the pulse rate 116 per minute. Microscopic examination of the exudate from the eyes revealed Gram-negative diplococci of morphology characteristic of gonococci. No abnormality was noted on examination of the blood or urine. The rectal temperature varied from 100.6° to 99.6° F. during the first three days of the infant's stay in the hospital. On the fourth day all evidence of conjunctivitis had disappeared. The infant was afebrile and accepted his food. Early on the morning of the fifth day the infant passed two large green stools that contained blood and mucus. During the remainder of the day numerous small liquid stools were evacuated. The rectal temperature became elevated to 100° F. Oral feeding was discontinued for 24 hours and 5 per cent glucose in saline was administered subcutaneously. The specimen of feces yielded *S. anatum*. During the next day the baby expelled five brown semisolid stools. Boiled skimmed milk was given and subcutaneous fluids were discontinued. The maximum rectal temperature was 99.8° F. The boiled skimmed milk was given on the following day, during which time the temperature was normal. The patient was returned to a regular diet on the eighth day and appeared to be normal during the remainder of the hospital stay.

CASE 4.—J. K., a 7-month-old Negro male infant, was admitted to the hospital for treatment of bronchopneumonia, duration six days. At the time of admission on March 1, 1945, the rectal temperature was 104.6° F., the pulse rate was 200, and the respiratory

rate 56. The throat was slightly injected. Respiration was predominantly abdominal, the breath sounds were accentuated in the base of the left lung and were accompanied by a slight friction rub. The infant breathed in a gasping manner. Urinalysis revealed normal findings. The hemoglobin was 9 Gm. per cent, and red cell count was 4,940,000, the white blood cell count was 23,500. Therapy consisted of oral administration of sulfadiazine and general supportive measures. The patient's general condition appeared to improve rapidly. On the fifth and sixth days the infant rested and ate well and had no abnormal temperature. However on the seventh day the rectal temperature reached a maximum of 102° F. and a minimum of 100° F. Five liquid yellow stools were expelled in 24 hours. Culture of the stool yielded *S. anatum*. The urinalysis revealed no abnormality. Two grams of sulfaguanidine were given as the initial dose and was followed by 1 Gm. every four hours. The diet was changed to boiled skimmed milk and supplementary vitamins. Physical examination of the chest revealed no abnormality. At least four liquid stools containing blood and mucus were noted on the eighth hospital day. The rectal temperature varied from 101° to 103.4° F. The infant appeared to be in good general condition with no signs of dehydration or acidosis. Two semisolid stools free of blood were noted on the following day. The temperature ranged from 101° to 103° F. The infant vomited a small amount of one feeding. On the tenth day the rectal temperature and the bowel movements were normal. The infant was returned to an evaporated milk diet. During the next 72 hours he appeared to be normal. The sulfaguanidine was discontinued on the twelfth day. The infant lost no weight during the hospital stay and was discharged on the thirteenth day.

CASE 5.—A 5-month-old Negro female was admitted to the hospital on March 1, 1945, for treatment of a transverse fracture of the femur of one month's duration. With exception of the fractured femur, physical examination revealed no abnormality. An x-ray examination of the long bones gave evidence of scurvy. Examination of the blood and urine revealed normal findings. The patient was placed in Bryant's extension, was given a normal diet for her age plus large doses of ascorbic acid and other supplementary vitamins. She pursued an uneventful course until March 7, when she passed three green liquid stools during a period of 24 hours. The stools contained mucus but no blood. Since the diarrhea was mild, the dietary regime was not altered. A stool culture yielded *S. anatum*. The rectal temperature was slightly elevated during a 4-hour period reaching a maximum of 100.4° F. On the following day the stools were normal in number but still liquid. The remainder of the hospital stay was uneventful.

#### DISCUSSION

On the basis of clinical manifestation, salmonella infections tend to be in one of the following categories:

1. Paratyphoid fever
2. Septicemia
3. Gastroenteritis
4. Carrier state

Considering the genus as a whole there is considerable overlapping in the clinical manifestations produced by the various species. Except for the paratyphoid group, this overlapping is so irregular as to make any association between species and clinical type of disease appear fortuitous. Bornstein and Schwarz<sup>16</sup> noted that the salmonella belonging to groups B and C caused the more severe type of disease. Hormaeche and associates<sup>17</sup> have classified the clinical types of enteric fever in three groups: (1) the dysenteriform type characterized by colic, "low" localization, frequent passage of stools containing mucus, pus, and often blood, and usually a high fever; (2) the choleric form

type, characterized by profuse watery diarrhea, the stools not containing pus or blood; and (3) mixed type. Here the process starts as one type and subsequently changes to the other type. The cases of enteritis described in this paper resemble Hormaeche's dysenteriform type. Although blood and pus were found in the stools in the cases here described, the disease was mild in nature and response to treatment was fairly prompt.

It is of interest to note that in seven of the cases some type of respiratory disease occurred. Although the number of cases is too limited to warrant definite conclusions, the question naturally arises as to the role played by the respiratory infection in lowering resistance and thereby paving the way for salmonella infection.

Bornstein<sup>18</sup> mentioned that sulfaguanidine was effective in controlling some salmonella infections, but not all. In the present series it was found that sulfadiazine given for treatment of the respiratory infection did not prevent the development of enteritis.

*S. anatum* is a member of Group E<sub>1</sub> based on the determination of somatic antigens present in the cell. In its pathogenicity for man it is most frequently associated with gastroenteritis, more rarely occurring in septicemia, cholecystitis, and meningitis. Kauffmann cites three deaths in a series of 28 cases, a mortality rate of 10.7 per cent. This is probably exceptional.

From the literature covering *S. anatum* one reaches the conclusion that it is world-wide in distribution. Man is afforded the opportunity of acquiring the infection from diseased and perhaps healthy animals and fowls. Its presence in meat products suggests another possible source of infection as shown by Cherry, Scherago, and Weaver.<sup>5</sup> Another possible source of infection is human carriers<sup>2, 8, 10, 11, 12, 14</sup> especially if they are food handlers. In the present study the source of infection remains obscure. Hormaeche and associates<sup>17</sup> have isolated *S. anatum* from flies at irregular intervals. The mild weather at the time our cases occurred permitted the ingress of flies even in March. The fact that a flock of experimental ducklings was kept in the vicinity of the hospital at the time the cases occurred suggests that insect transmission may have occurred. The probability of a carrier among the food handlers at the hospital was not excluded entirely, since only one stool specimen from each attendant was cultured, with negative results. However, since the infection was limited to one ward, it seems more likely that the mode of transmission was from patient to patient and that only those of low resistance contracted the enteritis.

#### SUMMARY

1. Although infection with *S. anatum* is relatively uncommon, eight cases were observed during a period of thirteen months.
2. The clinical picture presented by five cases was that of enteritis characterized by elevation of temperature, mild diarrhea, and the appearance of mucus and blood in the stools soon after the onset of symptoms.
3. The disease was of short duration.

The authors are indebted to Dr. P. R. Edwards of the National Salmonella Center, Lexington, Ky., for serologic identification of the species.



## REFERENCES

1. Rettger, L. F., and Scoville, M. M.: J. Infect. Dis. 26: 217, 1920.
2. Edwards, P. R., and Bruner, D. W.: J. Infect. Dis. 72: 58, 1943.
3. Hormaeche, E., and Salsamendi, R.: Arch. urug. de med., cir. y especialid. 14: 375, 1939.
4. Rubin, H. L., Scherago, M., and Weaver, R. H.: Am. J. Hyg. 36: 43, 1942.
5. Cherry, W. B., Scherago, M., and Weaver, R. H.: Am. J. Hyg. 37: 211, 1943.
6. Varela, G.: J. PEDIAT. 25: 555, 1944.
7. Kauffmann, F., and Silberstein, W.: Zentralbl. f. Bakt. (Abt. 1) 132: 431, 1934.
8. Bornstein, S.: J. Immunol. 46: 439, 1943.
9. Bornstein, S., Saphra, I., and Strauss, L.: J. Infect. Dis. 69: 59, 1941.
10. Galton, M. M., and Quan, A. L.: Am. J. Hyg. 38: 173, 1943.
11. Galton, M. M., and Quan, M. S.: Am. J. Pub. Health 34: 1071, 1944.
12. Seligmann, E., Saphra, I., and Wassermann, M.: Am. J. Hyg. 38: 226, 1943.
13. Rubenstein, A. D., Feemster, R. F., and Smith, H. M.: Am. J. Pub. Health 34: 841, 1944.
14. Stone, W. S.: Am. J. Pub. Health 33: 706, 1943.
15. Kauffmann, F.: Die Bakteriologie der Salmonella-Gruppe, Kopenhagen, 1941, Ejnar Munksgaards.
16. Bornstein, S., and Schwarz, H.: Am. J. M. Sc. 204: 546, 1942.
17. Hormaeche, E., Surraco, N. L., Peluffo, C. A., and Aleppo, P. L.: Am. J. Dis. Child. 66: 539, 1943.
18. Bornstein, S.: New York State J. Med. 42: 163, 1942.

# TREATMENT OF EPIDEMIC DIARRHEA OF THE NEWBORN

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THE term, "epidemic diarrhea of the newborn," refers to a disease occurring in newborn nurseries, characterized by the passage of frequent, watery stools, body dehydration, and varying toxicity, with a tendency to involve many infants simultaneously.

## ETIOLOGY

This disease has increasingly forced itself on the attention of the pediatricist in recent years. Despite its frequency and high mortality, the causative agent has escaped certain identification. The work of Light and Hodes<sup>1</sup> and of Buddingh and Dodd<sup>2</sup> indicates that a filtrable virus is responsible for some epidemics. In an occasional epidemic, pathogenic bacteria are cultured from the stools.

## EPIDEMIOLOGY

The epidemiology is still obscure. There is suggestive evidence that the causative agent is transmitted from infant to infant by way of nurses and doctors caring for them. Buddingh and Dodd demonstrated that, in one epidemic, the causative agent could be isolated from the mouths of apparently well nurses and doctors, indicating that carriers may be an important factor in the transmission of this disease.

## PROPHYLAXIS

Prophylaxis of epidemic diarrhea aims at minimizing exposure of well infants to sources of infection. The dramatic disappearance of secondary cases of diarrhea at The Cradle in Evanston<sup>3</sup> suggests that rigid precautions can prevent transfer of the causative agent by personnel in attendance and by equipment.

Two observations of Light and Hodes raise the hope that prophylaxis by biologic means may be discovered. These workers produced diarrhea in calves with filtrate of stools from epidemics in newborn infants. After recovery, these animals were immune to further inoculation. Second, Light and Hodes demonstrated that some infants, recovered from epidemic diarrhea, had protective factors in their serum.

The work of Buddingh and Dodd indicates it may be possible to detect carriers by oral swabs applied to the scarified cornea of a rabbit.

## TREATMENT

The treatment of epidemic diarrhea of the newborn has several objectives:

1. Direct attack on the causative agent

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2. Relief of the diarrhea, per se
3. Correction of the disturbances in physiology caused by diarrhea, especially dehydration, disturbances of acid-base equilibrium, and vasomotor collapse
4. Maintenance of metabolic needs until the patient is well enough to tolerate a normal diet

*Attacks on Causative Agent.*—At present no method is at hand for a direct attack on the causative agent of this disease. The presence of a virus in some epidemics may explain why sulfonamide therapy has not been impressive. This opinion is borne out by our own observation.

In the absence of specific therapy, reliance must be placed on symptomatic treatment. The following plan of therapy for a severe case of epidemic diarrhea of the newborn is not inflexible nor is it necessarily the most effective, but it has been successful in our experience.

*Relief of the Diarrhea.*—Checking the diarrhea itself is best achieved by giving the patient nothing by mouth. Starvation is continued until the infant stops passing stools for at least twelve hours, or longer if necessary. Usually the frequency of stools decreases markedly during the period of starvation. The duration of starvation is usually twenty-four to thirty-six hours, but occasionally longer.

The decision to begin feeding by mouth is of critical importance, and must be individualized in each case. One requirement is absence of stools for twelve or twenty-four hours. The more severe or prolonged the diarrhea was, the longer should be the period free from stools before resuming oral feeding. A second requirement is return of the blood serum carbon dioxide content to normal. A third is marked improvement in physical findings.

Sterile tap water is used for the initial feeding. It is offered at frequent intervals, in small and gradually increasing amounts: 5 or 10 c.c. at the first feeding, increased by 5 or 10 c.c. every two or three hours thereafter. The increments are continued until the amount offered equals 150 c.c. per kilogram for twenty-four hours. At this point, water is cautiously replaced by a formula. Skimmed lactic acid milk may be substituted for water in increments of 5 or 10 c.c. per feeding. The increments are continued until the amount offered equals 150 c.c. per kilogram per twenty-four hours which provides 60 calories per kilogram. From this point on, a milk of higher fat content, for example, half-skimmed lactic acid milk, is gradually substituted for skimmed lactic acid milk in quantity sufficient to raise the caloric intake by 10 calories per kilogram per day. This low fat formula is fortified by the gradual addition of carbohydrate until 120 calories per kilogram per day are provided. Meanwhile, the number of feedings is reduced to six daily. The formula is then gradually replaced by one which can be easily provided at home.

As a rule, there is no recurrence of diarrhea during this gradual return to a normal caloric intake. A few loose stools may be noted during the first two or three days after starting water by mouth.

*Replacement Therapy.*—The disturbances of physiology caused by the diarrhea include vasomotor collapse, dehydration, and acidosis. Anemia and low serum proteins are commonly observed. It is conceivable that other metabolic errors are present which elude detection in the present state of our knowledge.

Methods to correct the distorted physiology are directed chiefly at increasing blood volume, restoring renal function, and correcting dehydration. These methods may be called "replacement therapy." Replacement therapy is both quantitative and qualitative.

The total amount of parenteral fluid needed is estimated chiefly from physical findings. The well-known signs of dehydration appear when fluid loss approximates 8 to 12 per cent of the body weight (80 to 120 c.c. per kilogram). However, as much as 20 per cent of the body weight may be lost daily during a very severe diarrhea. To supply maintenance as well as replacement needs, 200 to 250 c.c. of total fluids per kilogram parenterally are usually sufficient in the first day or two of starvation. The clinical response is a useful guide here. One looks for gain in weight, resumption of urinary flow, and disappearance of signs of dehydration.

Guideposts to qualitative replacement therapy are provided by history; physical signs, and initial blood chemistries. If the blood serum carbon dioxide content is under 35 volumes per cent, sodium lactate solution may be desirable. It is prudent to use two parts of physiologic sodium chloride solution to one part of one-sixth molar sodium lactate to preserve the normal relationship of sodium and chloride ions and prevent alkalosis. Elevated serum chloride on admission suggests poor kidney function, due, in most instances, to poor renal blood flow. After the amount of sodium lactate and saline has been estimated, the remainder of the fluid is given as 5 or 10 per cent glucose. Serum proteins are generally regarded as a good index of dehydration but their concentration at times is normal on the initial determination, only to fall below normal (e.g., to 5 Gm. per 100 c.c. or less) after fluids are given. A normal concentration of serum proteins on admission may be misleading in two respects: (1) it may wrongly suggest that dehydration is slight, and (2) it may mask a real hypoproteinemia which appears when dehydration has been corrected. The hemoglobin and red cell count may be wrongly interpreted.

In concrete terms, replacement therapy may be initiated as follows: A specimen of blood is drawn for determination of carbon dioxide content, serum chlorides, and serum protein. Where a free flow of blood is obtained, urea nitrogen is measured.

If the patient is very dehydrated, a clysis of physiologic saline, 40 c.c. per kilogram, is started, and an infusion of 10 per cent glucose, 20 c.c. per kilogram, is given during or immediately after the saline clysis. If the patient is in collapse the infusion should be started first and followed promptly by a clysis. When the physical findings suggest severe acidosis, one-sixth molar sodium lactate solution may be used in place of part or all of the saline in the clysis.

The combined effect of the two treatments is an increase in blood volume, improvement in renal blood flow and renal function, and partial repair of the sodium and water deficit. Clinically, these effects are manifested by improvement in the state of consciousness, activity, color, and cry. The signs of dehydration regress somewhat. Soon after these initial treatments, a transfusion of whole blood or plasma, 20 c.c. per kilogram, is administered. At this point, replacement therapy is well under way.

*Maintenance Therapy.*—The transition from replacement therapy to maintenance therapy is a gradual event. As each measurable factor returns to normal, our future aim is to maintain it at normal. As the diarrhea improves, from 1 to 1.5 Gm. of sodium chloride in an isotonic solution are given per day, parenterally. The level of serum chloride aids in gauging the dosage. Plasma infusions are given to maintain the total serum protein at 5.5 to 6 Gm. per 100 c.c. Water is continued at the rate of 175 c.c. per kilogram for a day or two, and usually reduced thereafter to 150 c.c. Five per cent glucose solution constitutes the greater part of the fluid administered during maintenance.

The fluid requirements are given in four separate treatments per twenty-four hours, usually in the form of two clyses and two infusions. Plasma or whole blood transfusions are given in addition.

It is imperative that parenteral fluids be continued after starting water by mouth, first to maintain an adequate fluid intake during the slow increase in the oral feeding, and second to supply glucose. At this stage, after a prolonged diarrhea, collapse due to hypoglycemia is occasionally seen.

Amino acids in maintenance therapy theoretically should be valuable. When starvation is prolonged or diarrhea recurs, the patient may be treated with Amigen. A clysis of 5 per cent amigen and 5 per cent glucose is well tolerated twice daily. Two infusions of 5 per cent glucose, in addition to these clyses, will provide 45 calories per kilogram per day. If one of the 5 per cent glucose treatments is given in saline, it will provide 1 Gm. of sodium chloride for the newborn infant of average weight. It is well to recall Hartmann's warning<sup>4</sup> that poor peripheral circulation, or very low serum proteins, is a contraindication to the use of a hypertonic clysis such as 5 per cent amigen and glucose.

It is prudent to administer certain vitamins during starvation. If the diarrhea or the starvation is prolonged, vitamin K should be administered in some form. In very prolonged diarrhea it is probably well to repeat an injection of vitamin K according to the level of prothrombin. Bleeding because of hypoprothrombinemia has been demonstrated in diarrhea in young infants. Ascorbic acid 50 mg., thiamin chloride 3 mg., riboflavin 2 mg., and niacinamide 10 mg. may be given by infusion daily. Larger doses are used in prolonged diarrhea.

Occasionally an infant continues to have diarrhea in spite of starvation of four or more days' duration. In such a case, the prognosis is poor whether starvation is continued or feedings are started in spite of the diarrhea. Recent experience suggests that the outlook for these infants is improved when

amigen and glucose are administered parenterally to provide 45 or 50 calories per kilogram daily in place of or in addition to oral feedings. Why these intractable cases do not respond to starvation is not clear. Perhaps the natural body defenses have not destroyed the causative agent of the diarrhea.

Another obscure question is why such patients die despite the usual restoration of chlorides, protein, serum carbon dioxide, and hemoglobin to normal levels by therapy. This repeated observation suggests that the infant has a disturbance in physiology which we cannot now measure. Butler, McKhann, and Gamble<sup>5</sup> stated in 1933: "Parenteral therapy has a large, often dramatic, effectiveness. It must be admitted, however, that it is not always successful and it may be hoped that recognition of an additional pathologic process in the situation will eventually produce supplementary measures which will provide a more complete control of the severe stage of diarrheal disease." In the same article these authors demonstrated that infants in an advanced stage of diarrhea excreted intracellular fluid "to an extent much greater than can be accounted for by release of water due to destruction of protoplasm," and referred to the desirability of replacing intracellular materials including potassium. More recent laboratory observations indicate that loss of intracellular potassium results from water depletion from various causes.<sup>6\*</sup>

#### RESULTS

Between Jan. 1, 1940, and Dec. 31, 1944, ninety-one full-term infants under 4 weeks of age were treated by this method with twelve deaths, a mortality rate of 13 per cent. Of ninety-two premature infants similarly treated in the same period, there were eighteen deaths, a mortality rate of 17 per cent.

#### SUMMARY

The treatment of epidemic diarrhea of the newborn is still symptomatic and consists of relief of the diarrhea by starvation; correction of dehydration, acidosis, vasomotor collapse, anemia, and hypoproteinemia by parenteral fluids; maintenance of metabolic needs until the patient can tolerate a normal diet by mouth; and a very gradual resumption of a normal caloric intake orally.

#### REFERENCES

1. Light, J. S., and Hodes, H. L.: *Am. J. Pub. Health* 33: 1451, 1943.
2. Buddingh, G. J., and Dodd, K.: *J. PEDIAT.* 25: 105, 1944.
3. Sauer, L.: *J. PEDIAT.* 6: 753, 1935.
4. Hartmann, A. F., Lawler, H. J., and Meeker, C. S.: *J. PEDIAT.* 24: 371, 1944.
5. Butler, A. M., McKhann, C. F., and Gamble, J. L.: *J. PEDIAT.* 3: 84, 1933.
6. Elkinton, J. R., and Winkler, A. W.: *J. Clin. Investigation* 23: 93, 1944.
7. Darrow, D. C.: *J. PEDIAT.* 28: 515, 1946.
8. Goran, C. D., and Darrow, D. C.: *J. PEDIAT.* 28: 541, 1946.

\*Since this paper was submitted for publication, Darrow has reported the successful administration of potassium, in larger amounts than previously used, in diarrhea in infants.<sup>7,8</sup>

## BEHAVIOR ASPECTS OF THE CARE OF THE PREMATURE INFANT

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TO compress this subject into brief space, I shall limit my remarks to viable fetal infants, that is, preterm infants with postconceptional ages of from 28 to 40 weeks. And I shall interpret the psychology of these infants in terms of their muscle tonus, as observed in some 80 developmental examinations.

Tonus is a key concept, because tonus *is* behavior. Tonus is a condition of muscle tension, mediated by both the autonomic and cerebrospinal nervous systems. It varies with the concentration of free acetylcholine—a humoral substance which has been demonstrated to be “highly electrogenic” at the site of liberation. In this sense tonus is a property of living tissue. The dead, we are reminded, have no tonus. The dying are losing tonus. The weak have low tonus.

Therefore, at the threshold of viability all measures which safeguard and foster the function of tonus are of critical importance in the care of the premature infant. The behavior hygiene of the premature infant consists in the maintenance of optimal tonus.

What is optimal? We do not know, because the phenomenon of tonus has not been adequately studied by clinical methods. Tonus is not simply a by-product of internal and external conditions of temperature, humidity, body fluids, and metabolic level. It reacts to these factors, and can be partly controlled through them; but it has its true origin in the structural maturity of the organism. The fetal infant himself initiates the primary tonal responses. These responses organize with age. In the young, or early stage, fetal infant (fetal age 28 to 32 weeks) muscle tone is at a low level. It has three characteristics: it is fluctuant, patchy, and precarious. In the mature, or late stage, fetal infant (36 to 40 weeks) the tone has risen to a higher level. It is relatively steady, consolidated and sustained. It is also more obviously patterned and adaptive.

Tonus is patterned through growth processes, and it should be managed on a developmental basis. It is not a generalized quality or quantity which merely increases in magnitude. It is an architected mechanism which is built into the growing nervous system.

In the youngest fetal infants tone is minimal, flaccid, and uneven. It rises, falls, and shifts above its low level. It may be comparatively high in one region, and low in another. As tonus tires it seems to “wander” to fresher areas. This

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This paper is based in part on observations reported in *The Embryology of Behavior*, Arnold Gesell, M.D., in collaboration with Catherine S. Amatruda, M.D., New York, 1945, Harper and Brothers, p. 289.

meandering characteristic is probably related both to morphogenetic factors and to the physiologic mechanism of recruitment.\*

Even in the midstage fetal infant the tonal responses are more integrated. His gross postural activity comes in configured waves rather than in small localized ripples. His general tonus increases on manipulation and rises to meet limited emergencies. He is not as fragile as he seems; but his tone does peter out readily.

The late stage, near-term fetal infant has more tone on tap. He does not need to husband his tone as formerly, because he has reserves of it to draw on. The whole substratum of tonus is more consolidated; he seems more firmly knit into a single, sturdy piece. He is more nearly ready to meet the buffetings of fate.

Now this progression toward organized tonus is the essence of the psychology of the fetus and of the premature infant. His mental life is mainly one of kinesthesia and tactility. His mental health has less to do with seeing and hearing. It has much to do with the satisfactions of bodily movement, and the ancient sensorium of skin and mucous membrane.

We can reach his psychic needs more fully by more adequate methods of routine care and management. I shall briefly indicate practical possibilities under four headings: (1) clothes, (2) cleansing, (3) handling, and (4) bedding.

*Clothes.*—Birth deprives the fetal infant of the snug investment of the uterus. It is idle to duplicate intrauterine conditions; but it is not impossible to restore some of their advantages. The modern neonate does not take kindly to nudity, even in a humidior. I believe that he craves the tactile and the thermal snugness of clothes. This suggests that there are virtues in a close-fitting, long-sleeved pique jacket, in cotton batting booties wrapped about the feet and pindling lower legs with a strip of soft cloth, and a diminutive steamer-robe envelope which bundles the torso, but leaves the arms free. Tender subjects may need a bonnet as well. Ensconced papoose-fashion in such an investment, the fetal infant may be presumed to feel more at home. The comprehensive pressure upon all parts of his sensitive skin helps him to maintain a comfortable minimal level of tonus; and yet leaves him free to deploy his spontaneous, meandering tonal reactions. The slight variations in surface temperature would seem to be salutary.

*Cleansing.*—But he may also react favorably to the intensifications of stimulation which come with a brief warm bath, and a deft Dutch rub. The crying induced by the daily cleansing probably has a beneficial effect upon the pulmonary alveoli. Restored with dispatch to snug clothes the experience may well carry with it just the right amount of mild stimulation to contribute to the in-

\*It is important to remember that muscle fibers work in relays and that both in muscular tonus and in active muscular contraction the method of recruitment prevails. Not all fibers are called and chosen at once. They are recruited by squads. This principle of recruitment is reflected in the progressions of embryogenesis. If we could witness the whole sequence of events we could see relays of recruitment in successive areas of circumscribed tonicity and in sporadic and partial contractions. But there comes a time when enough neuromotor structure has been built up to bring about a palpable movement of head and trunk. That time marks the beginning of observable overt behavior.



fant's developmental welfare. The vigor of the ministrations must, of course, be tempered to the vigor of his tonal reactivity. The complete avoidance of all such stimulation leads to the opposite danger of depressing isolation. There is a hygienic medium between excessive caution and injudicious handling.

*Handling.*—The fetal infant is not as fragile as he is supposed to be. He needs skillful handling rather than no handling at all. If he were still in the uterus, he would have the benefit of jolting, jarrings, impacts, changes in position, and travel with the activities and goings and comings of the mother. Does he not miss these experiences when he is immobilized day in, day out in an incubator?

The clothing already described makes it possible to manipulate the infant with a greater degree of safety, and to provide him with needed translations in space, stimulating his semicircular canals and his kinesthesias.

Handling should be brief, because tonus readily tires; but if it is dextrous and done with dispatch, the fetal infant is likely to acquire a quality of hardiness instead of the softness which necessarily comes with unmitigated hospitalization.

*Bedding.*—Even the bed of the fetal infant may be too soft and too stationary. The uterus is not only a garment but a bed which moves with the postural adjustments of the active mother, and even with her respirations as she sleeps. On these grounds one can make a psychological case for a mattress of resilient material, suspended on sensitive springs which yield to the stirrings of the infant. Responsive bedding imparts a sense of movement and may have a favorable effect on the development of body tone.

The foregoing arrangements tend to personalize the care of the premature infant. Under the acculturating influence of one or two months of such care he may make consistent progress. In uncomplicated cases prematurity does not disturb the normal course of development. The healthy premature infant does not acquire any unnatural precocity from his head start; neither does he suffer any setback. This should be a great comfort to his anxious mother. She should be assured that the healthy premature infant follows the basic sequences of normal mental growth, making due allowance for his spurious age.

Fortunately, the maturational insurance factors are so strongly entrenched that they protect the fetal infant to a great degree even from faulty methods of care. But if we are to bring his potentialities to the highest realization we must study more closely his total behavior economy by clinical methods of observation. His psychological needs are most clearly manifested in his basic muscle tonus and his patterns of tonal behavior.

# CONGENITAL ADRENAL CORTICAL INSUFFICIENCY ASSOCIATED WITH MACROGENITOSOMIA

## FOLLOW-UP AND TERMINAL REPORT

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THE case of congenital adrenal cortical insufficiency with macrogenitosomia reported in 1941<sup>1</sup> has been observed for six years and to the time of death with measles on Nov. 17, 1945. The interim story and the final study of the case are reported for the purpose of making available to others the data of one more case of a disease entity still poorly understood.

R. M., a male child, the third of normal, healthy, Italian-American parents, was born on Nov. 18, 1939, weighing 7 pounds 10 ounces. The first child of the family, a boy 10 years older, is living and well; the second child, who was born in 1935, died at 5 weeks of age with symptoms similar to those of the patient. The birth of R. M. was essentially normal. The child was put to breast according to hospital routine every three hours during the day and every four hours at night. The mother had an abundant milk supply, and the infant nursed well but failed to gain. For this reason a supplementary formula was started on the seventh day. On the eighth day the weight dropped an additional 5 ounces, and the stools became frequent and green, and contained large amounts of mucus. The baby was isolated; normal salt was given by clysis; and a change of formula was made. Stool cultures revealed no pathologic organisms, and the subsequent character and consistency of the movements did not suggest an infectious origin. There was no fever. The child took his food poorly, vomited frequently, and was very listless. Diets with and without breast milk and various formulas were tried without avail. Transfusions, intravenous glucose, and normal saline by clysis were necessary to sustain him. When parenteral fluid was omitted for one period of thirty-six hours, the patient went into collapse requiring oxygen and stimulants, as well as fluids. A gastrointestinal series was done to rule out partial obstruction, such as stenosis or volvulus.

After two weeks of therapy the patient's apparent daily need of parenteral saline suggested the possibility of adrenal insufficiency as the underlying pathology. A more careful inquiry then revealed that the sibling who had died had exhibited symptoms similar to those of the patient, and a diagnosis of probable adrenal insufficiency had been made but was not confirmed since the family refused permission for an autopsy. The child had a hypospadias and probably was a female pseudohermaphrodite.

Administration of per cortin was started on December 29, 0.3 c.c. being given hypodermically daily. His progress from then on was considerably better except when we resorted to experimentation. Since there was no guiding precedent and it was unknown whether or not spontaneous improvement might occur, successively gradual reduction of the dosage of per cortin was tried, and administration of adrenotropic hormone to stimulate the adrenal cortex was employed, plus use of salt in the diet. However, it always became necessary to resort eventually to subcutaneous saline and per cortin given hypodermically to restore him to balance. Therefore, the mother was taught to give the drug injections at home, and the patient was dismissed, to be followed in the outpatient department.

At 6 months of age enlargement of the genitalia was unmistakable; pubic hair and a low voice were noted shortly thereafter.

In August, 1940, at 9 months of age, the patient was admitted to the hospital because of vomiting and fever. A diagnosis of exanthem subitum was made, and recovery was uneventful. An intravenous pyelogram revealed no abnormalities in the kidneys. Bone age studies showed the lower, but not the upper extremities to be advanced.

<sup>1</sup>From University of California Hospital, Pediatrics Department and Children's Hospital, San Francisco.

While the patient was in the hospital, desoxycorticosterone acetate for sublingual administration was supplied by Dr. Evelyn Anderson, and the patient was given 2 drops under the tongue four times daily (4 drops or 1 mg.). This dosage subsequently was increased to five times daily, and finally to 4 drops five or six times a day. The child remained well, gained weight regularly, and had a good appetite. When the new method of administration was first tried, he was restless and consumed, at times, excessive quantities of water. It was then determined that with these symptoms he needed more of the drug, and the mother varied the amount accordingly.

At 14 months of age the patient's weight was 24 pounds 12 ounces; height 82 cm.; bi-iliac crest 13 cm.; anteroposterior and lateral chest, 11 and 16 cm., respectively; sitting height, 50 cm.; and span, 77 cm. The penis was 7 cm. long, and some pubic hair was present. His bone age was that of a 3-year-old child. His fontanel was closed. He had four teeth. He walked holding on to objects, said a few words, and was bright and alert. When receiving adequate desoxycorticosterone acetate, he was happy, but if the dosage were reduced, he was restless and irritable, had a poor appetite, and drank excessive amounts of water, 10 or 15 ounces daily. Even at these times he had no craving for salt; opportunity to show such a preference had been given him innumerable times since early infancy. His diet was regular for his age and well fortified with vitamins. He showed no abnormal trends in his appetite except that he rather consistently refused sweet foods. This was not marked enough to attribute it to a peculiarity of his disease.

Further hospital admissions for acute illnesses were: .

From Sept. 27 to Oct. 2, 1941, with the diagnosis of convulsion with upper respiratory infection. At this time the child had his first convulsion, a moderately severe one. The illness was treated with sulfathiazole and he continued with the sublingual therapy during the entire illness.

He was in the hospital from Dec. 10 to Dec. 18, 1942, at the age of 3 years, with a diagnosis of right upper lobe pneumonia, confirmed by x-ray. He had had a convulsion prior to admission with this illness. His white blood count was 36,600, with 71 per cent polymorphonuclears. He made an uneventful recovery on chemotherapy.

He was again in the hospital from Oct. 28 to Oct. 31, 1943, at the age of 4 years, at which time he had a tonsillectomy and adenoidectomy with uneventful recovery.

The final admission was Nov. 16, 1945. The following day he expired. The diagnosis was measles with convulsion. The story of his terminal illness is: On Nov. 15, 1945, he had a temperature rise to 100.4° rectally, with a hacking cough. The mother noticed that his throat was slightly red and his eyes were injected. On the morning of November 16, he awoke with a morbilliform rash and a temperature of 105°. He was seen by the physician at this time and a diagnosis of measles was made. Koplik spots were present. Shortly after the doctor's visit, he had a convulsion which lasted, with slight remissions, to the time of his death. At no time did he regain consciousness.

The physical examination on admission to the hospital was incomplete due to patient's condition. The temperature was 107.8°. He was unconscious, with intermittent convulsive movements. The lips were cyanotic and there was a maculopapular rash on the face and chest, heaviest near the scalp line. The nose and throat were filled with mucopus. Pupils were dilated; conjunctivae were injected.

The nose and throat were cleared by suction. He was given oxygen, phenobarbital gr. 2 hypodermically, and 5 per cent glucose and saline was started intravenously. This was interrupted after 500 c.c. had been taken and he was given 250 c.c. of normal pooled human serum, after which another 500 c.c. of 5 per cent glucose and saline were given.

At 6:15 p.m. the temperature was down to 102.7°, the color improved, and he was quieter. He died at 1:30 a.m. on Nov. 17, 1945.

*Laboratory Data.*—Complete blood count: hemoglobin, 106 per cent (15.4 Gm.); red blood cells, 5,470,000; white blood cells, 9,200; polymorphonuclear neutrophils, 59 per cent; nonfilament, 14 per cent; lymphocytes, 37 per cent; and unclassified, 4 per cent.

The following autopsy report was received from University of California Hospital:

### ANATOMIC DIAGNOSIS

- I. Bilateral adrenal cortical hyperplasia, extreme
  - A. Aberrant adrenal cortical rests in testis, bilateral
  - B. Macrogenitosomia
    1. Pubertas precox
    2. Adult body contour
    3. Hyperplasia of the prostate
  - C. Persistent thymus
  - D. Hypertrophy of the juxtaglomerular apparatus
- II. Measles (clinical)
  - A. Diffuse dermatitis (superficial lymphocytic infiltration)
  - B. Generalized lymphoid hyperplasia with focal necrosis and giant cell formation (Linkeldy type)
  - C. Acute tracheobronchitis
  - D. Bronchopneumonia

### GROSS DESCRIPTION

The body is that of a well developed, well-nourished white male child, appearing about 13 years old (although stated to be 6). He is 58 inches long and weighs perhaps 90 pounds. Body musculature is everywhere well developed, body contours are of adult type, and there is a well developed area of pubic hair. The penis is quite large, resembling that of an adult male. The neck is heavy and the throat large, so that the entire body contour is that of a well developed male. The lower extremities, however, are small in proportion. There is no icterus, no peripheral edema, and no palpable subcutaneous lymph nodes. Livor, rigor, and algor mortis are present. A rather coarse macular rash is present on the face and thorax. The skin is thin, subcutaneous fat is fairly abundant and of usual color, and muscle structure is quite heavy. There is no free fluid in any of the body cavities and the organs are normally disposed. The thymus is quite large, weighing 28 grams, and covering the upper half of the anterior mediastinum. The thyroid appears of usual size, weighs 14 grams, and shows no gross changes. Numerous large lymph nodes are present, those in the mesentery measuring up to 5 cm. in diameter. Each is discrete and, on section, red and translucent.

The heart is of usual contour and weighs 160 grams. The epicardium is smooth; myocardium is firm, red tan, striated, and measures 0.3 cm. on the right, to 1.1 cm. on the left. The endocardium shows no gross abnormalities, the valve circumferences being as follows: tricuspid 8 cm.; pulmonic 6 cm.; mitral 8 cm.; aortic 5 cm. Coronary ostia are patent and major coronary branches show smooth intima. The aortic intima is smooth. Vena cava and renal arteries are patent.

The lungs are of usual contour and weight, the right weighing 480 grams, and the left 340 grams. Pleural surfaces are smooth; outer surface is reddish, with numerous, somewhat firmer areas. The mucosa of the trachea and bronchi is extremely red and has adherent a moderate amount of thick material. The hilar lymph nodes are rather large and resemble those described in the mesentery.

The liver is of usual contour and weighs 1280 grams. The capsular surface is smooth; cut surface is yellowish and dotted with red. The gall bladder wall is delicate and extra-hepatic biliary passages are patent.

The pancreas and gastrointestinal tract show no gross changes.

The spleen is quite large. The capsule is smooth. The organ is firm and weighs 140 grams. Cut surface is reddish with prominent, translucent, whitish markings.

The adrenals are very large. The right weighs 38 grams, the left 36 grams. They are of the usual shape. However, on section, a very narrow yellowish peripheral zone is noted, the remainder of each gland being formed by firm, hemorrhagic tissue.

The kidneys together weigh 195 grams. The capsule strips with ease from a smooth surface. On section, cortex and medulla are distinct. The mucosa of pelvis, ureters, and

bladder is pale and smooth. The prostate is quite small and does not project into the prostatic urethra. The *testes* weigh approximately 4 grams each. They are quite small and show the usual epididymis. On section, in each testis there is a nodule of reddish tissue which forms a central mass, each about 1.0 cm. in diameter.

The scalp, skull, and meninges show no gross changes. The *brain* appears somewhat swollen, filling the dura mater.

#### MICROSCOPIC DESCRIPTION

*Brain:* The vessels of the brain show no changes. Section of the brain shows grossly normal cerebellum and pons. The ventricular system is of the usual dimensions and the brain shows no gross changes. The *pineal* is distinct and 0.5 cm. in diameter.

*Heart:* The myofibrils are definitely widened for this age. They show prominent cross striations. The nuclei are long oval to rectangular. The fibrous tissue is likewise diffusely increased and a few small coronary radioles show somewhat thickened intima.

*Lungs:* The vessels throughout are greatly distended. Many areas of lung contain extravasated blood. Larger regions, however, are filled with polymorphonuclear leucocytes which form plugs within small bronchi.

*Liver:* There are no changes of note.

*Pancreas:* There are no changes of note.

*Spleen:* The sinuses are filled with blood. An occasional Malpighian body shows a small area of necrosis. In one, a multinucleated giant cell is noted.

*Thymus:* Several intact Hassall's corpuscles are noted. There are several small collections of epithelial cells. In one of these, a zone of necrosis is present.

*Urinary and bladder:* There are no changes of note.

*Skin:* Sections of skin from the thorax show collections of lymphocytes about small capillaries in the superficial derma. A few inflammatory cells are also noted about skin appendages.

*Trachea:* The mucosa is intact. Beneath it, small vessels are enormously dilated and there are numerous lymphocytes and a few plasma cells. These extend to the underlying cartilage. A moderate number of polymorphonuclear leucocytes are present as well. This reaction is seen in small bronchial radicles as well.

*Lymph Nodes:* Lymph nodes from various areas show essentially similar changes. Follicles are poorly preserved, germinal centers often disintegrated. However, there is a diffuse increase of lymphocytes throughout the nodes and occasionally there are small nests of large, pale cells suggestive of reticulum. Some of these show minute foci of necrosis. At the borders of these, an occasional large cell is noted, containing fairly abundant eosinophilic cytoplasm, the whole cell perhaps 40 micra in diameter and containing clustered central nuclei, perhaps as many as 20.

*Kidneys:* The glomeruli and cells show no changes, the capillaries being well filled with blood. However, the juxtaglomerular cells both in the glomerulus and in the distal tubules are quite large, appear increased in number, and form a prominent part of the glomerulus. The walls of afferent arterioles are of usual thickness, the tubules show no changes, and the walls of large vessels are of usual dimensions.

*Testes:* Tubules show a rather flat lining with no evidence of formation of spermatogonia. The grossly noted tumor masses are composed of sheets of cells which are poorly demarcated from surrounding testicular tissue. At the margin, this tissue surrounds an occasional tubule and appears to be extending into near-by tissue. In these regions there are occasional clumps of lymphocytes. The central areas are composed of a rather scant fibrous stroma which separates groups of large polygonal cells which are heavily demarcated and show rather abundant eosinophilic cytoplasm and round finely reticular nuclei. These cells are suggestive of adrenal cortex.

*Thyroid:* There are no changes of note.

*Parathyroid:* The glands are quite small and composed of masses of uniform cells which occasionally form small acini. These cells show scant cytoplasm and round, hyperchromatic nuclei.

*Prostate:* The stroma is quite scant. There are numerous, fairly large glands which show occasional folding of their lining. The lining for the most part is of a single cell thickness and composed of a simple cuboidal type cell.

*Adrenals:* The two glands are essentially similar. Each shows an intact capsule in which occasional clumps of lymphocytes are noted. The tissue is composed primarily of cortex which forms multiple, irregular nodules as well as a diffuse, extremely wide cortical zone. These cells are similar throughout the thickness of the cortex, no medullary tissue being identified. The cells are quite large, polygonal, and heavily demarcated with abundant eosinophilic, granular cytoplasm, occasionally containing yellow-brown granules. Nuclei are round, hyperchromatic, and show large nucleoli. Mitotic figures are not noted. Stain with Ponceau-Fuchsin.

*Pituitary:* The pars nervosa shows no change. There is a cystic area completely surrounded by glandular tissue (which in addition forms a fairly large mass). This tissue is in usual arrangement for anterior lobe and shows a marked predominance of alpha cells.

## COMMENT

The parents of this child have been very cooperative, which has made it possible to follow satisfactorily his growth and development. In Table I are listed the weights and measurements taken at about yearly intervals. Complete

TABLE I

DATE	AGE		HEIGHT (INCHES)	WEIGHT (POUNDS)	TEETH	BONE AGE	SEXUAL DEVELOP- MENT	REMARKS
	MONTHS	YEARS						
11/18/39	Birth			7 $\frac{5}{8}$				
4/15/40	5		25	13				
8/ 8/40	9			23	4	Advanced	Penis 5 cm.; pubic hair	Exanthem subitum with convulsion
11/18/40	12	1	30 $\frac{1}{2}$	22 $\frac{1}{2}$	8			IV urograms neg- ative
1/18/41	14					3 yr.	Voice low	Walking; training
8/18/41	21		35 $\frac{1}{2}$	33 $\frac{1}{2}$	16		Advanced	I.Q. 104
10/ 6/41	23		36	36 $\frac{1}{2}$				Blood sugar 74 mg.; blood cho- lesterol 441
11/24/41	24	2	38	38	18	6 yr.	Erections	ECG negative
12/ 8/41	25		38 $\frac{1}{4}$	38 $\frac{1}{4}$	18			Pneumonia
3/ 2/42	27		40	43	20			
5/ 4/42	29		42 $\frac{1}{2}$	44 $\frac{1}{2}$	20			BP 80/40
7/27/42	32		43	47				I.Q. 110
10/12/42	36	3	45	50	20	8 to 9 yr.		ECG negative
4/19/43	41		48	58	20			Tonsillectomy and adenoidectomy
5/19/43								BP 90/40
							27 mg.; 17- ketoster- oids	Acute tonsillitis
8/ 2/43	45		49 $\frac{1}{2}$	60				
10/30/43	47 $\frac{1}{2}$	4						
12/18/44	61	5	56	75 $\frac{1}{2}$	Lost 1 lower inci- sor	10 yr. 11 yr.		Hemoglobin 120; RBC 6,000,000
11/ 1/45	71 $\frac{1}{2}$	6	57 $\frac{1}{2}$	88				
11/17/45	72	6			No 6-year molars			Died with measles

measurements were made but only the height, weight, and a few other pertinent remarks with regard to development are given in the table. Chart I expresses more graphically the growth and development of the child.

In addition to body measurements, yearly bone age studies and several electrocardiographic studies were made. Mental ratings were taken at two different times and interviews were held with a psychiatrist from time to time regarding the mental and emotional development of this child who physically showed a marked deviation from the normal children of his environment.

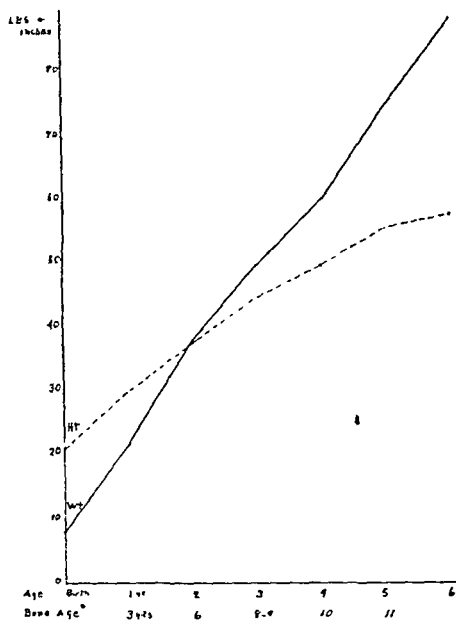


Chart I.—The height and weight curves from birth to 6 years of age and the corresponding bone age.

The table, chart, and pictures tell the story. It should be pointed out that his ultimate height, according to his scheme of growth, would have been below average. The epiphyses normally should have closed in another year or two. His ultimate height can be projected from the curve to about 5 feet. It should be noted that the facial contour, voice, and the appearance and distribution of body hair were that of an adolescent, but his testicles were small and undeveloped. His teething corresponded with his chronologic and not with his physiologic age. His feet, particularly, appeared somewhat undersize for the rest of his body, although he wore shoes the size for a 12- or 13-year-old, according to the mother's statement.

Mentally and emotionally the child was doing very well. He was in nursery school part of the time and played with the children of the neighborhood without any marked difficulty. This can be attributed to the cooperation of the parents and to their free discussion of the case with the pediatrician and with the mental hygienist. The nursery school understood the problem as did the neighbors, and it was handled in an intelligent manner by the adults in the environment. His need of hormone therapy was placed on the same basis as that



A. B. C.  
Fig. 1.—Illustrating the development of macrogenitosomia. A, 8 months old; B, one year old; C, 2 years old.



Fig. 2.—Illustrating the physique at the age of 5 years and 8 months.



of insulin for diabetes or thyroid for cretinism, and it was explained that this child's growth would be abnormal for a period of years until such a time as he would reach adolescence and would fit into the normal age group. The explanation was generally accepted, and was probably the basis for the normal mental and emotional development with a minimum of complexes in regard to the abnormality. It was felt that this phase of the child's development was of great importance inasmuch as the child's normal mental development and usefulness in the future would depend upon his adjustment to society, and any physical studies which were made would be made with greater assurance and satisfaction if his emotional and mental reactions were normal.

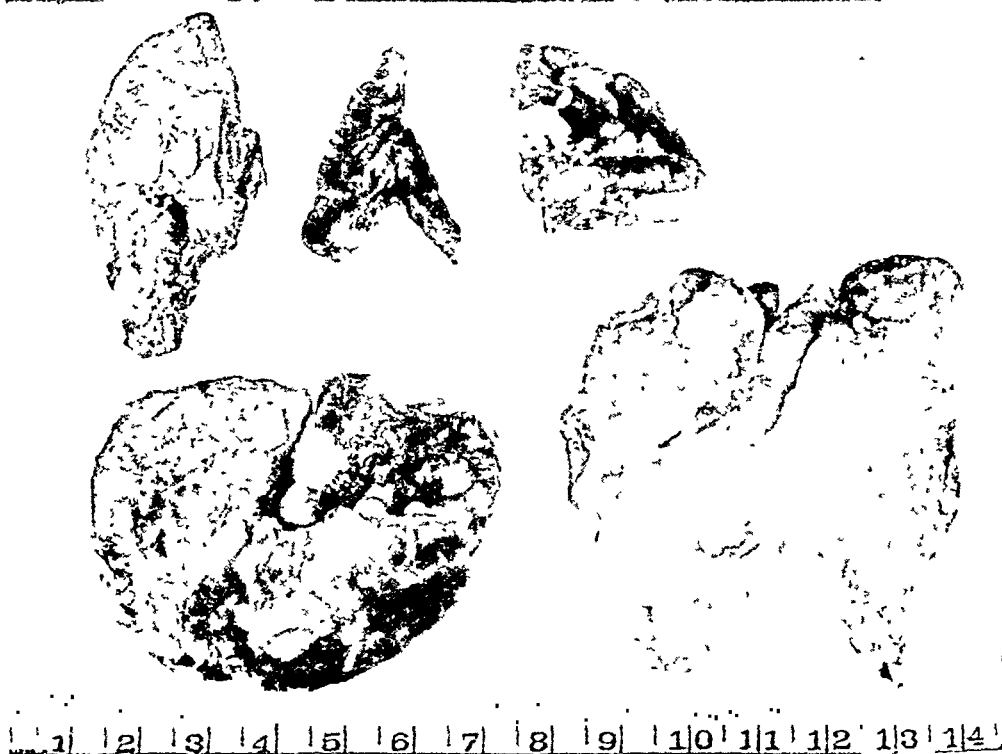


Fig. 3.—The adrenals compared with normal specimens.

A note received by the author from the mother, dated Nov. 1, 1945, states: "He has improved in his behavior and is more self-reliant and self-confident in his activities. He has also adjusted himself very well in school."

The lack of adrenal cortical hormone was adequately demonstrated several times during the child's span of life. At first it was withdrawn intentionally to see whether or not he could carry on normal metabolism without this hormone, and in this experiment we always failed and had to resume the use of the drug. On two or three other occasions, drugs that had deteriorated were used and the symptoms recurred, necessitating the examination of the drugs for potency and resorting to the use of fresh material. The presence of the androgenic hormone

is best illustrated in the growth of the child. This child was a husky boy, strong and energetic, and showed no evidence of any lack of hormone except when he became ill. His reactions to disease were always quite severe. He had two convulsions prior to the terminal one, and ran high temperatures with rather trivial infections. However, he had handled all of his other major illnesses with sufficient ease that it was entirely a surprise to the physician in charge when his measles infection proved so severe and uncontrollable.

The anatomic findings, as had been anticipated from a study of other cases of this type, showed a marked hypertrophy of the adrenal cortical tissue. He had bilateral adrenal cortical hyperplasia which was extreme and he had aberrant adrenal cortical rests in both testes. He also had a persistent thymus. Aside from this, the organs were normal. The striated muscle of the body and the muscles of the heart were normal for a boy of his size and development. The bony structure, teeth, and organs were well formed. This is remarkable inasmuch as the child grew with extreme rapidity. There was no evidence of lack of mineralization or avitaminosis.

The etiology of this syndrome remains obscure. The occurrence of the disease in siblings with no history of abnormality in the parents remains the challenging fact in etiology. The type of cell that constitutes the hypertrophied adrenal is still a subject for controversy. The type of secretion produced by this cell is still poorly understood. A clue to the etiologic factor is undoubtedly tied up with the fetal development of the adrenal tissue, the type of secretion which this tissue produces, and the change of this tissue from prenatal to post-natal life. The existence of some peculiar maternal-fetal interpathology is suggested. Incidentally, the parents were both Rh positive.

Reporting of these cases has continued to be low, which would indicate that either the incidence is low or that the patients die in infancy and the etiology is not recognized.

Sublingual therapy proved satisfactory and so simple for administration that it is to be recommended for trial in all these cases. There was no evidence that this patient was inadequately supplied by this method of administration. The only question that might arise is whether or not during an acute illness he would have fared better with large doses hypodermically or intravenously. This question will need further investigation. As far as the overproduction of androgenic hormone was concerned, there seemed no sound method of correcting this, because aberrant rests usually have been present in the testes, and bilateral removal of some of the tissue, therefore, would not have been a logical procedure. Adrenal tissue is not very susceptible to x-ray therapy.

Longer survival of these children can be anticipated in the future.

#### SUMMARY

A case of adrenal cortical insufficiency, congenital in origin and associated with macrogenitosomia, has been reported with details of the history, course, and autopsy findings.

#### REFERENCE

1. Thelander, H. E., and Cholfin, Mollie: J. PEDIAT. 18: 779, 1941.

## CONGENITAL AORTIC ATRESIA

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THE INCIDENCE of congenital cardiac anomalies varies from 5 per cent of autopsies done on infants alone<sup>1, 2</sup> to 1 per cent of autopsies performed on individuals in all age groups.<sup>3</sup> Of these, one of the rarest is the lesion to be described wherein complete fusion of the aortic cusps has occurred with resultant hypoplasia of the left side of the heart and ascending aorta. In the seven cases previously reported,<sup>6</sup> the maximum duration of life was fifteen weeks, the minimum two days, with an average of four days. Cardiac murmurs were heard in only two cases (one continuous throughout the cardiac cycle, the other systolic in time).

### CASE REPORT

Baby K., a white male infant, was delivered at term on Jan. 24, 1946, by low forceps. The birth weight was 6 pounds, 9 ounces (3 kg.). This was the mother's first pregnancy and it had been completely uneventful. There was no history of congenital heart disease in either the mother's or the father's family. There was no history of syphilis; the mother's serology was negative.

The baby was cyanotic and dyspneic at birth. The cyanosis increased in severity on crying. No murmurs were audible on auscultation of the heart and the lungs were described as negative. The baby was given carbogen and oxygen with temporary lessening of the cyanosis, but this soon returned and the baby expired January 26, approximately 48 hours after birth.

*Autopsy.*—Post-mortem examination performed seven hours after death showed a well-developed, well-nourished white newborn infant measuring 49 cm. in length. There was marked cyanosis of the lips and nail beds.

The principal pathologic findings were limited to the heart (Figs. 1 and 2). It weighed 18 grams (normal, 17 grams) and the epicardium was smooth and glistening. The aorta stemmed normally from the left ventricle and the pulmonary artery from the right, but there was a striking difference in size. The ascending aorta was narrowed, with a circumference of 0.6 cm. The pulmonary artery was dilated to a circumference of 1.9 cm. The aortic orifice was entirely closed by fusion of the valvular cusps and the finest probe could not be passed through it in either direction. The ductus arteriosus was widely patent and measured 0.5 cm. in circumference. Beyond the ductus, the remainder of the aortic arch and descending aorta assumed their normal caliber. The coronary arteries stemmed normally from the aorta and showed nothing unusual. A pronounced difference in size of the auricles and ventricles was also noted. The right atrium was markedly dilated and roomy, the left atrium shrunken to a mere vestige. The two atria communicated through a patent foramen ovale measuring 0.5 cm. in diameter. The left ventricle was atretic and the chamber measured only 0.7 cm. in diameter, while the right ventricular chamber was dilated to a diameter of 5.1 cm. The right ventricle overlapped and surrounded the left ventricle. Several moderately soft, grey-white areas, measuring to 0.5 cm. in greatest diameter, were scattered throughout the myocardium of both ventricles.

The remainder of the organs showed marked congestion, and the medullae of both kidneys were grossly hemorrhagic. There were a few atelectatic areas in the left lung and the right lung was completely collapsed.



Fig. 1.—Heart showing hypoplastic left auricle, ventricle, and ascending aorta. The probe is through the patent foramen ovale.

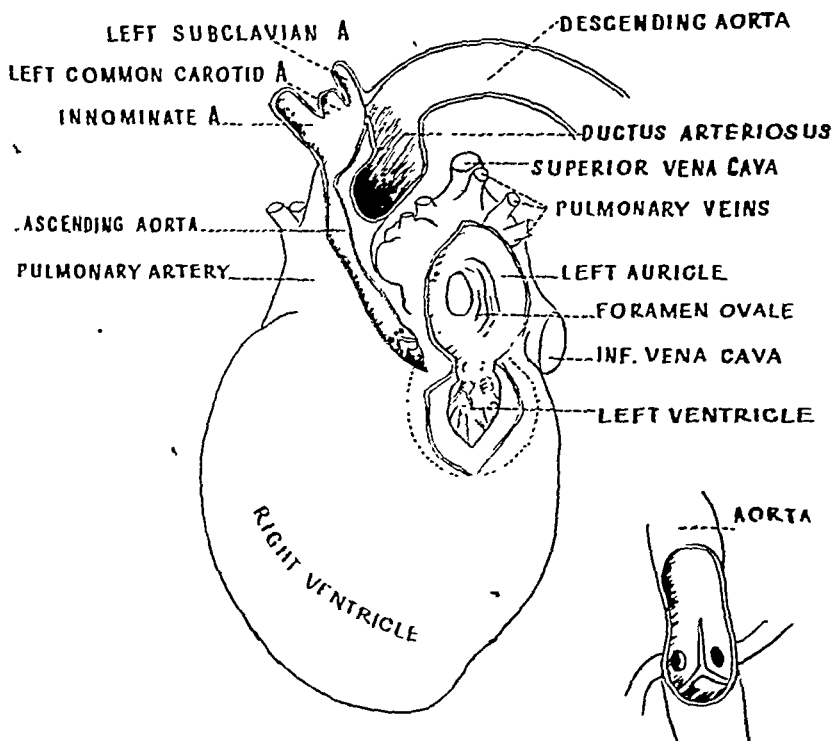


Fig. 2.—Schematic representation of the congenital anomalies of the heart in this case. (Drawing by Miss Annette Dorfman, adapted from a drawing of a similar case in Wesson and Beaver's article.)

*Histologic Examination*—Preparations from the heart showed numerous small areas and one large one in which the myocardium had been completely replaced by hyalinized fibrous connective tissue. No cellular infiltration was present in these areas (Fig. 3).

Examination of the remainder of the viscera showed passive congestion. In addition, there were hemorrhages in the kidneys, lungs, and thymus. The lungs revealed areas of atelectasis alternating with areas of emphysema. The left lung also showed hyalinized scars similar to those seen in the heart. The anterior lobe of the pituitary contained similar hyalinized areas. Extramedullary hematopoiesis was present in the liver.

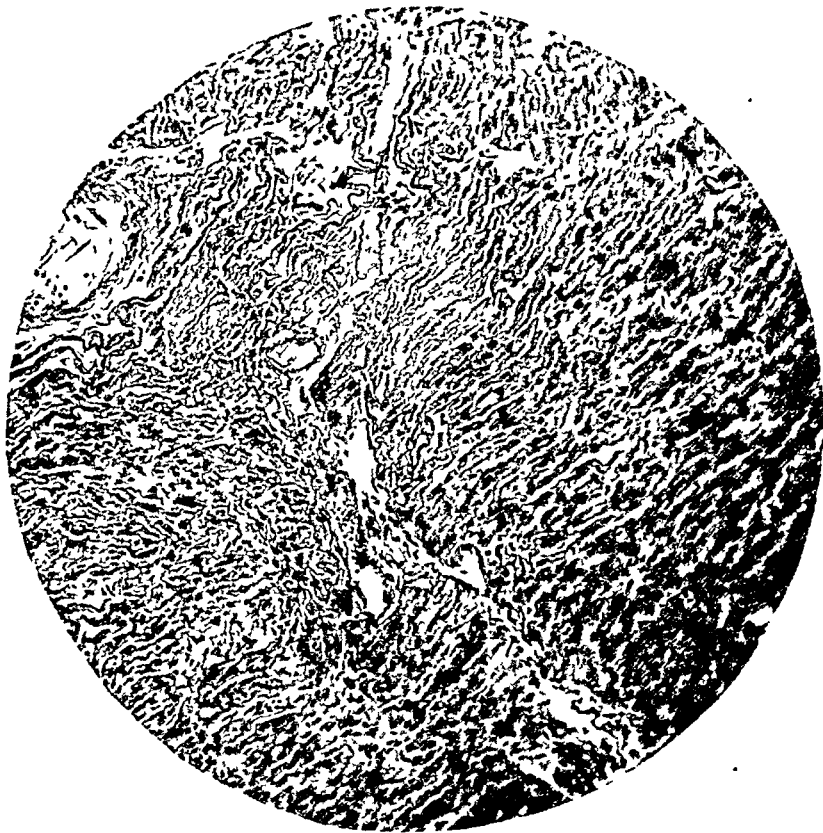


Fig 3—Photomicrograph of preparation from left ventricle showing hyalinized scars in the myocardium (H. & E  $\times 125$ .)

*Anatomic Diagnosis.*—Congenital defects in heart (fusion of aortic cusps; hypoplasia of left ventricle and left atrium; hypoplasia of ascending aorta; patent ductus arteriosus and foramen ovale); hypertrophy and dilatation of right ventricle and right atrium. Myofibrosis cordis; atelectasis and emphysema in lungs; scars in heart, lungs, and pituitary; hemorrhage in lungs, kidneys, and thymus; hematopoiesis, extramedullary, in liver; congestion of viscera.

#### DISCUSSION

Von Zalka<sup>4</sup> found (in cases of congenital pulmonary stenosis) vacuolation of the myocardial cells in the subendocardial region near the valve and infiltration with small round cells in this area. He believed the stenosis was due to

myocarditis and endocarditis during fetal life. Other observers<sup>5</sup> reported similar findings in cases of congenital aortic stenosis. In our case, the focal areas of scarring in the myocardium may be interpreted as healed fetal myocarditis. It can be assumed that infection of the aortic valve took place after formation of the heart had been completed, but early in fetal development while the organ was still small. With atresia of the aortic orifices proportionate growth of the left ventricle and ascending aorta ceased, so that at birth these units appeared as rudimentary or extremely hypoplastic structures. The right ventricle, of necessity carrying the entire circulatory load, became dilated and hypertrophied. Similarly, the ductus arteriosus was extremely large because it had been forced to perform not only its normal function but also that of the ascending aorta.

The left auricle and ventricle, obviously, were nonfunctioning. The blood reached the general circulation through the widely patent ductus, which also transmitted the blood in retrograde fashion to the coronary vessels. Blood entering the left auricle through the pulmonary veins, passed through the patent foramen ovale and then into the general circulation by way of the right ventricle.

#### SUMMARY

A case of congenital atresia of the aortic orifice, with widely patent foramen ovale and ductus arteriosus, and hypoplastic left auricle, ventricle, and ascending aorta is presented and the pathogenesis discussed.

#### REFERENCES

1. Gibson, S., and Clifton, W. M.: *Am. J. Dis. Child.* 55: 761, 1938.
2. Terplan, K., and Sanes, S.: *J. Tech. Methods* 15: 86, 1936.
3. Szypulski, J. T.: *J. Tech. Methods* 17: 119, 1937.
4. Von Zalka, E.: *Frankfurt. Ztschr. f. Path.* 30: 144, 1924.
5. Wesson, H. R., and Beaver, D. C.: *J. Tech. Methods* 14: 86, 1935.
6. Abbott, Maude E.: *Atlas of Congenital Cardiac Disease*, New York, 1936, The American Heart Association, p. 48.

## FOREIGN BODY IN DUODENUM CAUSING URINARY DISTURBANCE

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THE FOLLOWING case is reported because of the unusual findings associated with the presence of pyuria in a child, aged 2 years.

R. Q., 2 years old, male, was admitted to The Children's Memorial Hospital, June 22, 1945, with the following history:

In October, 1944, the child had a high temperature, nausea, and vomiting associated with a sore throat. At this time his urine was examined and found to contain albumin and pus cells. He was given medication and kept in bed. His temperature returned to normal but the urine continued to have albumin and contained pus and blood cells.

Since this time he had frequent bouts of temperature with sore throat. At these times the urine showed albumin and contained excessive numbers of blood and pus cells. After the temperature would drop, the albumin would decrease but the pus and blood cells would persist.

*Past History.*—Patient was the first child. There was no history of miscarriages. His birth was normal and he had had no serious illness except occasional upper respiratory infection. Development: First tooth erupted at 5 months; walked, 10 months; talked, 17 months.

*Physical Examination.*—Revealed a well-nourished and well-developed male child, 2 years old, not acutely ill. Physical findings were essentially negative. Abdomen was soft, no tenderness noted, nor were any masses palpable. External genitalia were normal. Urine: Slightly cloudy. Albumin 4 plus. Benzidine 2 plus. Microscopic examination showed no casts, numerous blood cells, and many pus cells.

*Cystoscopic Examination.*—Bladder essentially normal.

*Intravenous Pyelogram.*—(Fig. 1.) X-ray of the abdomen showed a bobby pin in the second and third portions of the duodenum. Films made at intervals after the intravenous injection of dye showed good visualization of the pelvis, primary and secondary calices, and ureters on both sides. Only the upper half of the right ureter was clearly set out and this appeared to be several times the diameter of the upper portion of the left ureter.

The finding of the bobby pin was a surprise. The mother was questioned and she did not recall the child having had choking spells or any difficulty in swallowing. How long the pin had been present in the duodenum was not known. The child was sent home for a further period of observation, in the hope that if the pin had been there only a short while it might pass.

After two weeks he returned to the hospital. Another x-ray was taken and the pin was found to be in the same position. He was admitted to the hospital preparatory to an exploratory laparotomy and removing the pin.

*Operative Procedure.*—On July 19, operation was performed under ether anesthesia. A right paramedian incision was made in the upper abdomen and the right rectus muscle was retracted laterally. Upon opening the peritoneum, extensive adhesions were seen between the transverse colon, inferior margin of the liver, and gall bladder. In fact, the hepatic flexure and proximal transverse colon were attached along the entire inferior margin of the right hepatic lobe and the gall bladder was not visible. Dissection was begun where the colon was adherent to the liver edge and continued downward until the duodenum was seen. Some periduodenal adhesions were then separated and the duodenum palpated. The foreign body (bobby pin) could be felt in the third part of the duodenum just proximal to the prominence formed by the vertebral column and it seemed to be rather firmly embedded.

Palpation of the right kidney in close proximity to the second and third parts of the duodenum revealed that the upper pole and renal pelvis were involved in the periduodenitis. There were many inflammatory adhesions in this region and the kidney seemed distinctly thicker and more fixed than usual. An attempt to gently manipulate the foreign body so that it could be pushed back into the stomach was not successful. The anterior duodenal wall was grasped with two Babcock forceps about one and one-half inches apart and a small incision in the longitudinal axis of the bowel was made. Through this incision a curved forceps was introduced with which the bobby pin was grasped and withdrawn.

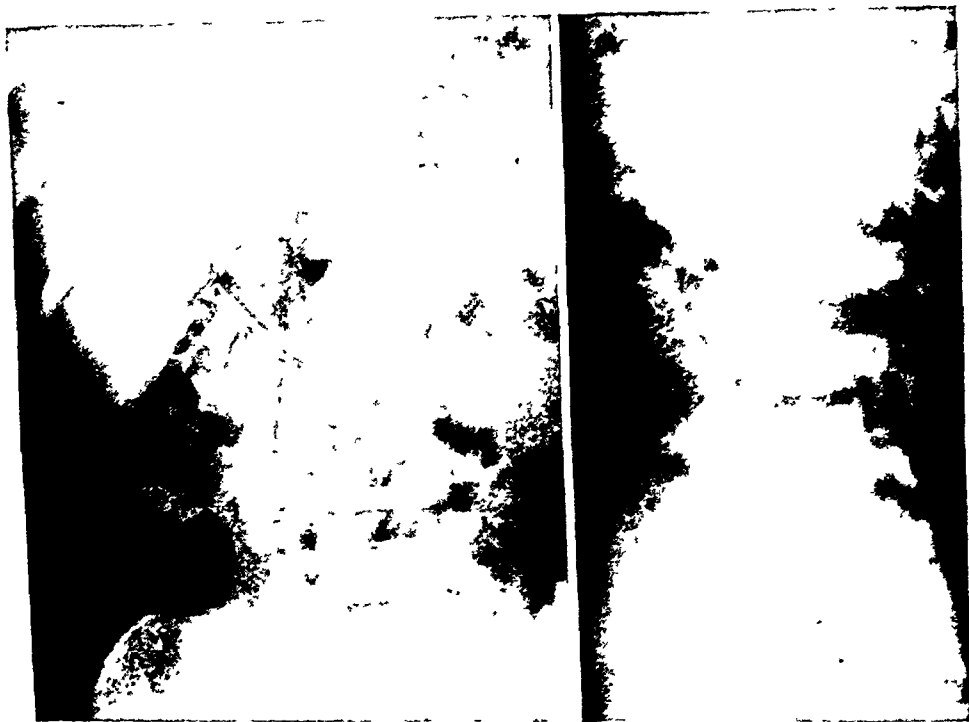


Fig. 1.—Lateral and anteroposterior views of abdomen showing bobby pin and dilated right ureter.

*Postoperative Course.*—The postoperative course was uncomplicated except for a small abscess which was evident at the upper end of the incision. This was evacuated on the seventh postoperative day and healing occurred promptly.

Specimen of urine on July 26 failed to show any albumin and no pus or blood cells.

Specimens of urine examined in August and September failed to show any albumin or any pus or blood cells.

#### COMMENT

Bobby pins, when swallowed by children, cause considerable trouble because they are a little too long to make the turn at the fixed portion of the duodenum. This case stresses the importance of a complete genitourinary tract study when albumin persists in the urine of a child. How long this foreign body had been present is not known but it possibly was causing trouble months before the original urinary trouble was noted in October, 1944.



# MALIGNANCY OF THE GENITOURINARY TRACT IN CHILDREN

## REPORT OF A CASE OF SARCOMA OF THE VULVA

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**G**YNECOLOGICAL tumors in infancy and childhood are not considered to be a common occurrence. Malignancy in the female genital tract in children is seldom, if ever, encountered.

In a review of the literature of some 1,500 cases of malignancy in childhood, we found about 0.1 per cent occurring in the genital tract. Most of the cases reviewed were reported as occurring in the eye, kidney, or bone. About 85 per cent of these proved to be sarcomas.

Wolff<sup>1</sup> in a survey of 11,000 cancer cases collected from several sources, found only 4.2 per cent in patients under 30 years of age. Kellert<sup>2</sup> found only 15 malignant growths in children under 16 years of age in a total of 2,050 malignant tumors of all kinds, or a ratio of one childhood tumor to 137 in adults. Simpson<sup>3</sup> reported the case of a botryoid tumor of the cervix in a girl 14 years of age. Knight<sup>4</sup> reported the case of a sarcoma occurring in the uterus of a girl 9 years of age. This was apparently treated successfully by roentgenotherapy. Kelly<sup>5</sup> gives an account of a melanoma of the vulva occurring in a child 14 years of age, which was treated by excision but resulted in metastasis and death two and one-half years after the onset of the first symptoms. Baldwin<sup>6</sup> excised a primary medullary squamous carcinoma of the vagina occurring in a girl 14 years of age. This was the only case, proved by microscopic studies, in a patient under 20 years of age in 905 cases of cancer found in the vulva, vagina, cervix and corpus. Glass<sup>7</sup> reported a case of sarcoma of the cervix in a girl 16 years of age, which was proved by microscopic studies. Ludwig<sup>8</sup> found a sarcoma of the cervix in a girl 16 years of age. This was treated by means of radium and x-ray therapy. Scheffey and Crawford<sup>9</sup> reported a case of adenocarcinoma of the cervix in an infant 22 months old. Lockhart<sup>10</sup> reported an extremely rare case of adenocarcinoma of the corpus uteri, which occurred in a child 3 years and 2 months of age. Taussig<sup>11</sup> removed a sarcoma of the vulva, which was somewhat similar to the case we are reporting. The original lesion was first noticed in the vulva when the patient was 7 months old, and grew gradually until surgically removed when she was 14 months old. Four months later, a tumor appeared on the opposite labium and surgical removal was again the procedure of choice. The tumor in Taussig's case proved to be a sarcoma of relatively low malignancy.

Malignancy of the female genitalia, occurring in children, is so rare that we feel justified in reporting this unusual case:

A white female, aged 3 years, was brought to the clinic because of a large mass protruding from the external genitalia. When the child was 13 months of age, bleeding from the vaginal orifice was noticed. Investigation by the mother revealed a small red, pea-sized

nodule just inside the labial fold. The bleeding was not severe and the nodule disappeared. At 16 months of age, a small nodule reappeared at the site of the original lesion. This did not bleed, but continued to grow—at first slowly and then began to protrude outside the labia. No medical advice was sought until the child began to lose weight. The mass was so large at that time that she was unable to walk.

The family history was irrelevant except for cancer of the stomach in the paternal grandfather. He was operated upon in 1941, and was in good health. There were three siblings living and well. There was no history of miscarriage or abortion.

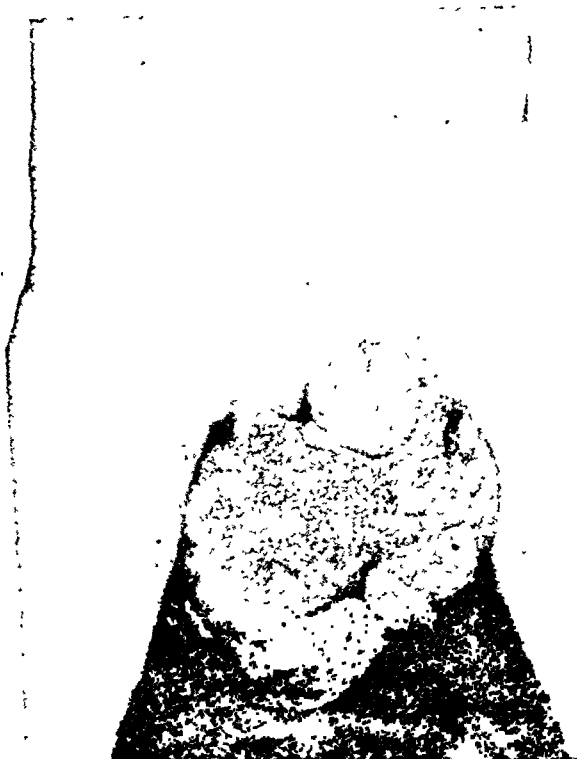


Fig. 1.

Examination revealed an emaciated child, tossing her head from side to side in apparent discomfort or pain. She responded to questions, but did not talk coherently. Her skin was dry and muscle tone poor, giving the appearance of rapid weight loss over a short period of time. Examination of the eyes, ears, nose, and throat did not show any abnormal findings. There was visible pulsation of the vessels of the neck. Cardiac impulse was seen at the left nipple line at the sixth interspace and was rather diffuse. No thrills were felt, and the heart rate was rapid and regular. There was a harsh systolic murmur heard over the precordium, more pronounced at the apex and transmitted to the axilla. Blood pressure was 110/95. Respirations were rapid and regular, and no râles or abnormal breath sounds were heard. The abdomen was distended, but there were no palpable masses and no apparent tender areas. Peristalsis was active. Protruding from external genitalia was a fungating tumor mass the size of a large grapefruit (Fig. 1). The surface was reddish, cauliflower-like in appearance, and covered with a reddish-gray exudate. It was impossible to determine the origin of the tumor because of its adherence to the external genitalia. On rectal examination there was no obstruction or abnormal findings. Urination was frequent, but it was impossible to observe

the external urethra or the opening through which the urine drained. The muscle tone was poor in the extremities, but she was able to move her arms and legs voluntarily. There were no sensory disturbances. The lymph nodes were not enlarged in any part of the body, and hardly palpable in the inguinal region. The skin was dry and rough, but there were no areas of discoloration, and no rash or skin lesions of any kind. Impression at this time was of a tumor mass of the external genitalia, probably malignant.



Fig. 2.

She was hospitalized and given a transfusion of whole blood. Penicillin compresses were kept constantly on the tumor mass. Methylene blue was given by mouth in an attempt to determine the location of the urethral orifice. The dye was excreted, but came from beneath the mass and we were unable to determine the exact location of the urethra. Attempts to pass a small rubber catheter through several of the crypts into the bladder were unsuccessful. Her general condition improved and her appetite was good. X-rays of the chest did not reveal any pathology in the lungs, and the heart size and shape were within normal limits. Blood count and urinalysis were normal. After one week of hospitalization, her condition had improved and surgical removal of the tumor was undertaken.

On June 4, 1945, under ether anesthesia, it was possible to carry out a more detailed examination prior to operation. The tumor was found to arise from the left labium minor by a rather wide pedicle. It completely filled the vagina and there was a large amount protruding outside. The urethra was displaced upward, forward, and to the right and was markedly angulated. An extension of the tumor was seen over the left side of the mons pubis.

An elliptical incision was made over the portion of the tumor which extended over the mons pubis and it was dissected free with ease. The incision was then extended downward into the vagina and into the left labium minor. The upper portion of the growth appeared to be encapsulated but the lower portion was dissected out with considerable difficulty as it infiltrated the left vaginal wall rather deeply. The resulting defects over the mons pubis and the vagina were sutured with interrupted chromic catgut. A retention catheter was placed in the bladder.



FIG. 3.

*Pathologic Report.*—The specimen consisted of two tumors. The larger measured 13 by 10 by 7.5 cm. and weighed 508 grams. It was reddish-yellow in color and its external surface was lobulated and friable. Its cut surface was white and its central portion firm. The smaller tumor measured 5 by 3 by 2.5 cm. It was covered by skin and appeared to be encapsulated. Microscopically, both tumors appeared essentially alike. They were composed of loose fibrous tissue which, in many places, appeared myxomatous. Throughout this were scattered many collections of large, polygonal cells arranged irregularly and varying in size and shape. Their nuclei were large, varying in shape from round to oval and there were many mitotic figures. (Fig. 2.) A diagnosis of fibromyxosarcoma was made. The sections were also studied by Dr. A. C. Broders, who confirmed the diagnosis, considering the tumor to be of grade two malignancy, according to his classification.<sup>12</sup>

*Course.*—The wound healed per primum. The retention catheter was removed on the seventh postoperative day, after which the patient voided and had good sphincter control. Her convalescence was complicated by persistent tachycardia, generalized edema, and accentuation of the pre-existing systolic murmur. However, the edema and tachycardia disappeared after the administration of digitalis. The patient was dismissed from the hospital June 17, 1945, on the fourteenth postoperative day with the wound completely healed. She was able to walk without assistance. (Fig. 3.)

The patient was readmitted to the hospital on June 29, 1945, with a history of acute retention. She was found to have a urethral stricture which was dilated under anesthesia.

The patient was next admitted Nov. 22, 1945. She had been feeling well, had been leading a normal life for a child of her age but had not gained weight and had had urinary incontinence for two months. Physical examination revealed moderate bilateral enlargement of the inguinal lymph nodes. On the left vaginal wall there was a red nodule measuring 0.5 cm. in diameter, which the mother stated resembled the original tumor. Roentgenogram of the chest was negative. There was no evidence of intra-abdominal extension of the tumor.

On Nov. 23, 1945, because of the lack of evidence of distant metastasis and the apparent localized involvement of the regional lymph nodes, bilateral radical dissection of the inguinal nodes was carried out, and the nodule in the vagina was excised.

Microscopic examination of the lymph nodes from the left side did not reveal any evidence of tumor. Those from the right side showed a small area of tumor which essentially resembled the original growth but was somewhat more cellular. The nodule in the vagina was granulation tissue and did not show any evidence of malignancy.

#### REFERENCES

1. Wolff, G.: *Ztschr. f. Krebsforsch.* 38: 409, 1933.
2. Kellert, E.: *New York State J. Med.* 39: 2259, 1939.
3. Simpson, E. E.: *Arch. Path.* 35: 535, 1943.
4. Knight, A. P.: *Bulletin, Guthrie Clinic*, October, 1939.
5. Kelly, John A.: *Cancer in Children*, Harold W. Dargeon, editor, St. Louis, 1940, C. V. Mosby Company. pp. 58-66.
6. Baldwin, L. G.: *Am. J. Obst. & Gynec.* 21: 728, 1931.
7. Glass, M.: *Am. J. Obst. & Gynec.* 26: 104, 1933.
8. Ludwig, D. B.: *Am. J. Obst. & Gynec.* 31: 536, 1936.
9. Scheffey, L. C., and Crawford, B. L.: *Am. J. Obst. & Gynec.* 24: 118, 1932.
10. Lockhart, H. A.: *Am. J. Obst. & Gynec.* 30: 76, 1935.
11. Taussig, F. J.: *Diseases of the Vulva. Gynecological and Obstetrical Monographs*, ed. 2, New York, 1931, D. Appleton and Company, vol. 13, pp. 127-133.
12. Broders, A. C.: Personal communication.

## A MODIFICATION OF THE BRECHT FEEDER

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**F**EEDING the infant with oral deformities or the physically or mentally inadequate child has always been a problem to the physician and nurse. This is especially true at the present time when, because of the shortage of trained help, the half-hour or more necessary to feed the infant must be cut to the minimum although an attempt must be made to satisfy the child's emotional as well as physical needs. The Brecht feeder is a type of bulb syringe to which a nipple can be attached and the milk drops into the infant's mouth as though he had secured it himself with normal sucking power. He swallows the milk and has the satisfaction of feeding in as nearly a normal manner as is possible. The modified Brecht feeder described here was designed primarily to meet the needs of these infants and to make it easier for the person feeding the baby. I have noted in many instances that an ordinary bulb syringe with a piece of rubber tubing attached is more successful than the Brecht feeder because the opening of this feeder is usually too small for an ordinary nipple to be attached, and the nipple furnished with most feeders is too long and narrow, causing the infant to gag or vomit, or else it wears out before the feeder does. In addition, one of the main advantages of a feeder is lost, namely, the satisfying of the sucking reflex.

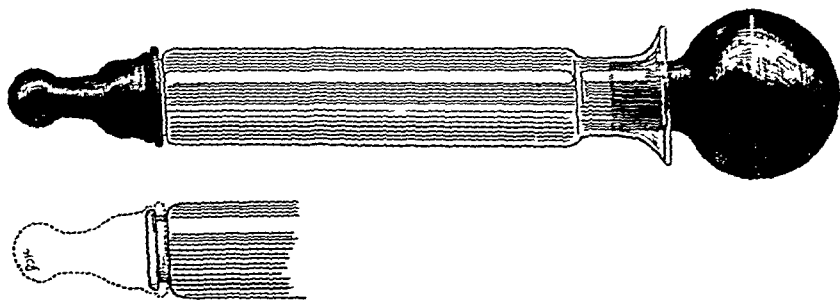


Fig. 1.

In correspondence with the research departments of various companies engaged in making infant feeders, I learned that they are under the impression that the feeder is used primarily for the premature or immature infant. This I do not believe is the case. It has been my experience that premature infants are usually fed by gavage or dropper if unable to nurse from a bottle. The greatest percentage of feeding problems occur in those infants who cannot create sufficient suction to nurse from a bottle because of weakness, oral

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deformities, or mental deficiency. In these infants gavage may be difficult because of the strong gag reflex or because of the danger of aspiration or of upsetting the infant physically and emotionally when feeding should give comfort and pleasure.

The feeder illustrated in Fig. 1 is designed like the Brecht feeder except that the opening is very much like the neck of an ordinary nursing bottle so that a nipple for a normal infant may be used. Most hospitals have two sizes of nipples, a larger for normal and a smaller for premature infants. Both fit this feeder, so either may be used. The glass is treated to withstand heat and is marked for measuring. It is my belief that this modification of the Brecht feeder should prove invaluable to those caring for infants who need the aid of this type of feeder.

The modified Brecht feeder described may be obtained from the Glasco Products Co., 11 North Canal St., Chicago, Ill.

# American Academy of Pediatrics

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## Proceedings

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### MEETING OF REGION I

HOTEL PENNSYLVANIA, NEW YORK, N. Y., APRIL 3, 1946

### COOPERATIVE NATIONAL PLANNING FOR IMPROVING CHILD HEALTH SERVICES

#### Panel Discussion

- Introduction. Stanley M. Nichols, M.D., Chairman, Committee on Cooperation With Governmental and Medical Agencies  
Representative of Council on Medical Service and Public Relations, American Medical Association. Louis H. Bauer, M.D., (Member of Board of Trustees, American Medical Association)  
Representative of the Children's Bureau, United States Department of Labor. A. Leonard Van Horn, M.D.  
Representative of United States Public Health Service. E. H. Coffey, M.D., United States Public Health Service  
Representative of the American Academy of Pediatrics. Joseph S. Wall, M.D., Chairman, Committee on Legislation

DR. STANLEY M. NICHOLS.—The greatest organization in this world today is the United Nations Organization. Peace, progress, and probably the survival of civilization itself depends on its success in developing real cooperation between the nations of this world. The greatest need in the American child health world today is to insure peace and progress by the voluntary, wholehearted cooperation of Government and medical agencies, working for better child health.

The greatest step forward the American Academy of Pediatrics can now take is the immediate sponsorship of a small national child health conference, meeting regularly, composed of the official representatives of the Federal and medical agencies working in the child health field.

Such a conference could study and promote definite existing areas of agreement, such as the present Maryland State Medical Society Plan, which uses governmental funds for families unable to provide good health care from their home resources.

Our committee's progress to date: Our Committee on Cooperation with Governmental and Medical Agencies, chairmaned by Dr. Martha Elliot of the Children's Bureau during the last two years, and your chairman has been the sufferer for the last seven and has worked steadily to promote the cooperation of the Governmental and medical agencies at both state and national level.

In case you are interested, copies of the State and National programs, approved by the Academy in 1941 and 1945 will be available at the registration desk at the end of this morning's session.

The Committee's program for the coming year: During the coming year, our committee will do three things. First, reactivate the State programs of our forty-eight State commit-



tees, who were doing first-class work before the war. Second, by request act as advisors to the Bureau of Food and Drugs of the Federal Security Administration as to drugs used in children, through a special subcommittee headed by Dr. Harold Murray of Newark. Third, and most important, promote our national program, particularly section four, which reads: "The Committee should aid in the formulation and coordination of the child health activities and program of Federal agencies, with those of the American Medical Association and the American Academy of Pediatrics. The Academy should sponsor a child health conference, meeting regularly, composed of representatives of the Federal and medical agencies working in the child health field to carry out this year this formulation."

On this panel you see for the first time in history the representatives of the four key Federal and medical agencies working in the child health field, voluntarily discussing cooperative national planning for improving child health service. In this key group, the American Medical Association represents the physicians of this country, the United States Public Health Service, public health, the Children's Bureau speaks for child health and welfare, and the Academy represents the pediatricians.

If our Academy, in its wisdom, now proceeds to sponsor a voluntary national child health conference of these agencies, empowered to confer regularly as to the formulation and coordination of improved child health service, of both Federal and medical agencies, we would immediately give a solid foundation to the growing American child health structure of the future. This would also provide, in the spirit of the Golden Rule, a practical means for the composition of divergent views as to methods of insuring better health for American children.

The pride and glory of our American democracy lies in the voluntary efforts of its citizens for the public good, made possible only by the exercise by free men of free speech, a free press, and the right of assembly. Superimposed on the health activities of our Governmental agencies are the splendid health achievements of our five national health professions and our twenty thousand voluntary health agencies.

Our national health is still the finest of any large country in the history of the world. This is true in spite of the present spring housecleaning of cobwebs from our twenty thousand voluntary health agencies by the National Health Council now under way and the streamlining of Federal agencies by the President and Congress.

Further improvement in child health services for American children largely depends on the voluntary, sincere cooperation of governmental and medical agencies, given factual expression from a working child health conference.

I trust our Academy will promote both peace and progress in our national planning for improving child health service by taking this essential step forward now. In the words of a great philosopher, "War, controversy, breed on suspicion. Peace walks hand in hand with truth and understanding."

**DR. LOUIS H. BAUER.**—Ladies and Gentlemen: I know you are primarily interested in pediatrics, but I think in order to tie in the pediatric problem into the general health problem, we will have to consider them together. So if you will bear with me, I am going to spend just a few minutes on the program of the American Medical Association as it pertains to health in general.

I think you are all familiar with the program which was announced last summer by the A. M. A.—the so-called fourteen-point program—many items of which have already become obsolete and have had to be changed. But briefly, the salient point of the program was the economic factor—that is, there is no question but that poverty breeds illness. But we feel that the answer, or the solving of the problem is not the pouring in of more medical care, but in the elimination of poverty, and that, of course, is an economic problem and not a medical one.

There are too few public health and preventive medicine facilities in the country, and it probably would not be possible for every county to have a full-time health department, because of, in some areas, scarcity of population and the expense. But we feel that neighboring counties could join together with a district health service and traveling laboratory, which

would cover, and where the states themselves could not afford to finance the entire project, the Federal Government could come into the picture. Also, there is an inadequate distribution of physicians, and one of the main reasons for that is inadequate hospitalization facilities and inadequate diagnostic facilities. The physician who is a good physician wants to remain such, and he cannot remain such unless he has the proper facilities to carry on his profession in the modern way. There again, where the states are unable, or the localities are unable to provide the necessary hospital and diagnostic facilities, the Federal Government can come into the picture, as is proposed in the Hill-Burton Bill, and the state is to retain control over the administration of these facilities.

Another point which is essential, and I think in any program we must bear in mind that you cannot pick out any one feature and say, "This is going to solve the problem," because it will not. It is everything together. It is the question of insurance. As you know, there are two schools of thought on that. One believes in the compulsory system, and the other believes in the voluntary system.

The A. M. A. has stood out for the voluntary system, holding that the compulsory system was not the American way of doing things, and that its experience with it elsewhere did not lead to the best type of medicine. I am not going to argue on compulsory insurance now. There is not time. I think you are all familiar with the arguments on it. But of course, the criticism of voluntary plans has been that they will not fill the bill, and they were not widespread enough. Of course, that second criticism, they were not widespread enough, I think has been justified. They have not been up to the present time, but that they will not, I think is not a fair criticism, because I do not think they have had the opportunity yet to show what they can do.

When this voluntary program was first suggested, no one knew anything about it at all. There was no actuarial background, and no one knew how the patients and doctors would react to it and what coverage should be given. Consequently, it was felt best to begin in a small way and experiment in various areas of the country to see what would work out and what would not; as a result of that, in the last number of years, a great deal of information has been obtained and now we feel we know pretty well what is required.

The American Medical Association has only last month set up a division of Medical Care Plans, with a director in charge, with the idea of stimulating the development of these plans where there are none at present and expanding those that are not yet covering great enough areas, and to give them help in every way, so that the whole country can be covered.

There are some twenty-seven states now that have these plans, and it is hoped that at the end of this year there will be forty states covered, and we hope in five years, or less, the entire country will be covered.

In addition to that, of course, we have many industrial plans and commercial insurance, so that a large percentage of the population is already covered in some degree—not as much as it should be and not as many people covered—but I think we have come to the point now where things are going to move fast.

I think you are familiar with the proposition in New York recently, where the Governor appointed a commission to investigate the question of health in New York State, and after two years of study, this Commission just rendered a report—or I better say reports; I think there are four altogether. They could not agree, but all but one man did agree that now was not the time to start compulsory insurance.

In any program we have to enlist the cooperation of everyone in order to make it work, and at the present time I do not think we are going to get the cooperation of the bulk of the medical profession in any compulsory plan—unless it can be definitely shown that the voluntary program will not work, which definitely has not been shown up to the present time. I mean this fourteen-point program. And in February, it was felt it was time to revise that, streamline it, and bring it a little more up to date, and that has been published. It is not very long, and as Dr. Nichols tells me he thinks many of you may not be familiar with it, I am going to read it to you. It is entitled "The National Health Program of the American Medical Association."

1. The American Medical Association urges a minimum standard of nutrition, housing, clothing and recreation as fundamental to good health and as an objective to be achieved in any suitable health program. The responsibility for attainment of this standard should be placed as far as possible on the individual, but the application of community effort, compatible with the maintenance of free enterprise, should be encouraged with governmental aid where needed.

2. The provision of preventive medical services through professionally competent health departments with sufficient staff and equipment to meet community needs is recognized as essential in a health program. The principle of Federal aid through provision of funds or personnel is recognized as essential in a health program. The principle of federal aid through provision of funds or personnel is recognized with the understanding that local areas shall control their own agencies as has been established in the field of education. Health departments should not assume the care of the sick as a function, since administration of medical care under such auspices tends to a deterioration in the quality of the service rendered. Medical care to those unable to provide for themselves is best administered by local and private agencies with the aid of public funds when needed. This program for national health should include the administration of medical care including hospitalization to all those needing it but unable to pay, such medical care to be provided preferably by a physician of the patient's choice with funds provided by local agencies with the assistance of Federal funds when necessary.

3. The procedures established by modern medicine for advice to the prospective mother and for adequate care in childbirth should be made available to all at a price that they can afford to pay. When local funds are lacking for the care of those unable to pay, Federal aid should be supplied with the funds administered through local or state agencies.

4. The child should have throughout infancy proper attention including scientific nutrition, immunization against preventable disease and other services included in infant welfare. Such services are best supplied by personal contact between the mother and the individual physician but may be provided through child care and infant welfare stations administered under local auspices with support by tax funds whenever the need can be shown.

5. The provision of health and diagnostic centers and hospitals necessary to community needs is an essential of good medical care. Such facilities are preferably supplied by local agencies, including the community, church, and trade agencies which have been responsible for the fine development of facilities for medical care in most American communities up to this time. Where such facilities are unavailable and cannot be supplied through local or state agencies, the Federal government may aid, preferably under a plan which requires that the need be shown and that the community prove its ability to maintain such institutions once they are established. (Hill-Burton Bill)

6. A program for medical care within the American system of individual initiative and freedom of enterprise includes the establishment of voluntary nonprofit prepayment plans for the costs of hospitalization (such as the Blue Cross plans) and voluntary nonprofit prepayment plans for medical care (such as those developed by many state and county medical societies). The principles of such insurance contracts should be acceptable to the Council on Medical Service of the American Medical Association and to the authoritative bodies of state medical associations. The evolution of voluntary prepayment insurance against the costs of sickness admits also the utilization of private sickness insurance plans which comply with state regulatory statutes and meet the standards of the Council on Medical Service of the American Medical Association.

7. A program for national health should include the administration of medical care, including hospitalization, to all veterans, such medical care to be provided preferably by a physician of the veteran's choice, with payment by the Veterans' Administration through a plan mutually agreed on between the state medical association and the Veterans' Administration.

8. Research for the advancement of medical science is fundamental in any national health program. The inclusion of medical research in a National Science Foundation, such as proposed in pending federal legislation, is endorsed.

9. The services rendered by volunteer philanthropic health agencies, such as the American Cancer Society, the National Tuberculosis Association, the National Foundation for Infantile Paralysis, Inc., and by philanthropic agencies such as the Commonwealth Fund and the Rockefeller Foundation, and similar bodies have been of vast benefit to the American people and are a natural outgrowth of the system of free enterprise and democracy that prevail in the United States. Their participation in a national health program should be encouraged and the growth of such agencies when properly administered should be commended.

10. Fundamental to the promotion of the public health and alleviation of illness are widespread education in the field of health and the widest possible dissemination of information regarding the prevention of disease and its treatment by authoritative agencies. Health education should be considered a necessary function of all departments of public health, medical associations and school authorities.

Now, in addition to that program, I think you are probably familiar with the fact the House of Delegates of the A. M. A. last December asked the Board of Trustees to investigate the advisability of establishing a national health congress, in which the various medical associations and organizations concerned with public health, and other organizations interested in the problem of health, should be brought together for national planning for the future in public health. That program is now in the throes of study, and we felt that there is not much use in establishing a national congress until we are assured of cooperation on the state and county levels. In the national organization, you cannot do the work; it must be done locally, no matter what you take, health or anything else. The real spadework must be done locally.

Consequently, a survey is now going on in all the states to determine what arrangements various localities now have for bringing together these various groups for handling local problems within the county or within the state, and as soon as that information is assembled, and also information as to what their plans are for developing this further, then it is hoped that some national get-together can be arranged. But I think it will have much more chance of success if we have assurance of cooperation on the lower level first and build it from the ground up, rather than from the top down.

DR. A. LEONARD VAN HORN: Dr. Eliot wished to have me express to you her regrets for not being able to be here today to attend the meeting and participate in the discussion. She, as you probably all know, has health hearings on health legislature now being conducted in Washington, and she felt it was important that she stay there. I gather from the morning paper that there is considerable heat down there. They apparently had a rather stormy session with the committee yesterday.

I really appreciate sincerely the opportunity of coming here and participating in this panel discussion. I particularly like the title for the topic, the first word particularly, which is "cooperation," and that is certainly what we would like to see more of.

During the past two years, I have also had the privilege of being a member of Dr. Nichol's committee and of working with them and considering the various methods of cooperation and how they can be worked out, both on the state and on the national level, and we hope something can come out of that.

I personally believe that this Committee carries one of the most important responsibilities in the Academy, and it can contribute to sound planning and development of an orderly and productive basis for cooperation between the Academy and all the Federal agencies concerned with the health and welfare of children, including the Children's Bureau.

My remarks are going to be pretty brief. I have felt it would be of perhaps even greater interest in the interpanel discussion that will follow, because I know, for example, I have a few questions that have come to my mind since Dr. Bauer has made his remarks. I think perhaps there will be others. But certainly, I think that we would like to see that interplay of thoughts and ideas after we hear these opening statements.

The Children's Bureau is the agency of the Federal Government which for more than thirty years has been given the responsibility by Congress for investigating and reporting upon all matters pertaining to the health and welfare of children among all classes of our people.

Since 1935, it has been charged with the responsibility for the administration of those sections of the Federal Social Security Act covering maternal and child health services, crippled children's services, and child welfare services. More recently, it was given responsibility for the administration of the emergency maternity and infant care program, a wartime measure enacted by Congress for providing help and medical care to wives and infants of enlisted men.

It seems appropriate, therefore, for the Children's Bureau to be concerned with any national planning designed to extend and improve health services for the nation's children.

Since 1914, the Children's Bureau has consistently sought advice and counsel from leading pediatricians in carrying out its functions. In fact, much of the credit for the progressive steps which have been taken by the Children's Bureau during the past thirty years can be attributed to the wisdom and vision of the many eminent pediatricians and obstetricians who have served the Bureau in an advisory and consultant capacity during this period.

Present conditions of child life in the United States, although superior to those in many countries, still leave much to be desired. Thousands of American children do not receive the amount or quality of health and medical services which they should receive in order to be assured even a minimum of health.

The importance of safeguarding the health of our nation's children cannot be overestimated. They represent our single greatest national asset and the hope of a peaceful world. This nation has the technical and the financial resources, if properly mobilized, to assure adequate health facilities and services for every American child. This requires planning and joint cooperative action by all communities, state and national groups concerned with the health and welfare of children. No one agency, organization, or professional group can assume full responsibility for such over-all planning. Public and private agencies, professional groups and lay groups must each play a part in developing the plan based solely upon the needs of children.

Many individuals believe that such a plan of action, to be effective, should not be submerged in a national compulsory health insurance system, but should be designed to meet the special needs of children. Many others believe that to finance medical care for children, partly through compulsory insurance is better, since it would provide for them the right to care that is inherent in such an insurance system and that supplementation of insurance funds with general surtax funds would assure coverage of those who wish to participate, noninsured as well as insured, and provide for the special services needed by children.

The first of these two concepts that I have mentioned here is exemplified in the Pepper Bill, the Maternal and Child Welfare Act of 1945, which was based upon recommendations of the National Commission on Children in Wartime. The latter idea is exemplified in S. 1606, which is the Wagner Bill, and the one that is up now for hearings before Senator Murray's committee.

We have in this country the knowledge and the resources to develop a comprehensive plan of action to meet the needs of children: What we need now is intelligent, cooperative national planning. The Children's Bureau is willing and glad to participate in such planning and to continue to carry out the mandate given it by Congress more than thirty years ago.

**DR. E. H. COFFEY:** It is a privilege for me to be here this morning as a representative of the United States Public Health Service. I say that with considerable pride. I have a feeling—and I feel justified in having a feeling—that the Public Health Service has played a very important part in improving child health of the nation. To be a part of the panel for planning for continued improvement of child health, it goes without saying that we are happy to have a part in such a discussion.

Before the turn of the twentieth century, we were given the responsibility by Congress of cooperating with the states in improving the state and local health services. That responsibility connoted, if you please, that the definite and direct responsibility rested with the local community or the state, that our job was to assist these communities and these states in meeting their responsibilities.

Throughout the years, we have adhered to that policy. Our practice has been always to cooperate with the state and local health departments, and in no sense usurp their prerogatives. Through some one hundred fifty or sixty years that the Public Health Service has functioned, there has been only one or two instances when we have had to step in and take over the responsibility of a local health department in a local area. Those were situations back perhaps a hundred years ago, when we had our epidemics of plague and yellow fever. Not since the time when we had great plagues in our nation has the Public Health Service felt it necessary to interfere in local health problems.

I say that to emphasize this one point, that with the number 2 item in the A. M. A. program—number 2, if you remember, is the recognition of the need for adequate health services throughout the nation. Now, we in the Public Health Service for a long time have recognized that need, and we have been working toward the goal of one hundred per cent representation or one hundred per cent coverage of local departments. Unfortunately, we have not attained that goal. Recent studies have disclosed that large areas in the United States are now still without the services of adequate local health departments.

Now, I am sure all of you will agree that no worth-while plan for improving child health can be evolved that does not give particular and specific attention to improving the over-all health services for the community; certainly, for the provision of full-time health service, so that environmental sanitation may be given consideration and control, so that the food-stuffs and milk supplies going to the population will be properly protected, so that communicable diseases will be under control, and so that the outstanding conditions or the more or less prevalent conditions, almost bearing upon epidemic proportions, can be given urgent attention.

Now, I do not desire, of course, to get into a controversy as to just what can be done in the development of full-time health services. However, I speak with considerable feeling this morning when I say that unfortunately, while we have had more or less lip service from the organized medical profession, and while we have had more or less acceptance of the principles that health departments were essential and necessary, we certainly have not had active support and cooperation on the part of the medical profession in bringing about this objective.

Now, when I say that, please understand that I recognize that in every single community of the United States today there are individuals who have gone all out to back up and to support full-time health departments. What I am speaking about is the organized effort of the medical profession—and I am sure that there is not a person in this room today who will not recognize and will not say that if the organized medical profession, on a community level, would get behind and actively support the inauguration of a full-time health service for their area or for their community, that that health department would come about this soon! At the snap of a finger.

After all, who should the people turn to in a community for leadership in the development of health services other than the medical profession? After all, who should the people listen to when the medical profession takes a more or less hands off attitude in the development of a local health service? Or whom should they be guided by?

I wish to throw this challenge today, as a part of this panel discussion, the challenge that where we have an area that does not have adequate full-time health services, the responsibility rests entirely upon the lackadaisicalness, we might say, of the medical profession, and I hope that the American Medical Association, in its national program, will give it the utmost attention, to develop that phase of their program—not merely word recognition, but active participation in bringing it about.

I have the feeling—and I think a good many of us in the Public Health Service have the feeling—that if today we had one hundred per cent coverage of our nation with full-time, adequately-trained, professionally-qualified public health personnel, that many of the controversies that are confronting us today, from the standpoint of the lapse or lack of medical care, and so forth, would not be present.

Now, so much for that. Without question, we can meet all of these problems. It would make a travesty of our democracy if we felt that they could not be met. And surely, the

governmental agencies, representing the people in the health field, have the responsibility and must lean upon the medical profession for guidance in meeting these problems. So as we go on now in our peacetime activities, forgetting the war, or problems confronted by the war, we are going to have to do a good bit like the United Nations Organization is doing today. We are going to have to overcome many obstacles, but we are going to have to continue to strive for that goal that we know will eventually come about—and that is the best of health for all the people in the nation. Thank you very much!

DR. JOSEPH S. WALL.—I have been asked to speak on behalf of the Academy of Pediatrics in relation to this subject. This discussion on cooperative efforts in national planning for improving child health services was conceived and prepared to present to the members of the Academy for their thoughtful consideration of problems of imminent importance which should not only command their interest, but enlist their aid in solution.

It was intended to be informative, through the presentation from authoritative sources of the role of participation in cooperative endeavor of four most important groups, governmental and medical, whose interests lie in the same sphere, whose objectives are mutually intertwined in official and civilian endeavor and whose activities should be, no doubt can be, cemented in an harmonious whole by considered discussion with resultant collective agreement.

It is fervently to be hoped that in the months to come, private initiative with governmental assistance to supply certain needs, where need is demonstrated, may fairly and adequately provide health services to the ultimate satisfaction of all concerned. Such provisions for better medical care for children, as well as for the adults of our nation, must possess the attributes of justice and equity to each of the segments of the population involved, whether they be the recipients of medical services, the ministers through whom such services are rendered, or the tax-paying public, who must be called upon in no small measure to provide funds through the public purse in cases of need.

To possess this needed and basic element of justice and equity, future medical planning should be formulated only after conference between all three members of the triangle named, for unilateral action, planned or put into actual operation by one single component of the triangle might possess the potentiality of such injuries and disharmonies to the other groups, that disaster would ultimately be the only outcome. Such directful results can much better be avoided by anticipation, rather than receive belated rectification in retrospect.

In relation to child health, pediatricians may point with satisfaction to the benefits which have accrued in the past from the various authoritative White House Conferences initiated in 1930, in which many of our members participated. Why could not a similar series of congresses or conferences to secure a meeting of minds be instituted in the immediate future?

Recent trends have indicated that a national health conference has an appeal which is receiving wider and greater support with each passing month. Even our limited effort of this morning's session is but a straw in the wind which reveals a growing current of belief in the wisdom of conferences and exchange of opinion concerning health planning. Many of our own beliefs will be crystallized after the report of the Academy's Committee on Child Health Services now engaged in an extensive study of which you will hear more later in the morning.

The Academy of Pediatrics, to the best of my knowledge, is the only medical organization which has had for many years a "standing committee" on cooperation with governmental and medical agencies, under the auspices of which this discussion is being conducted.

The committee consists not only of Academy Fellows, but in cooperative association includes official representatives appointed by the American Medical Association, the Children's Bureau of the United States Department of Labor, and by the United States Public Health Service, who are intimately concerned in the problems which engage our own attention.

The Academy itself has always pled for cooperation with all whose interests are concerned with children. To such has the Academy's aid ever been freely proffered and usually well received.

At its last meeting in Detroit, the Academy reiterated its eagerness to join in conference with those responsible for certain contemplated planning affecting the medical care of children. After lengthy discussion of pending congressional legislation, a resolution was unanimously adopted which reads as follows:

The American Academy of Pediatrics in annual session at Detroit, Michigan, January 15-18, 1946, after careful consideration of proposed legislation in Congress as it relates to child health services reaffirms its resolution as adopted at its 1939 session, namely:

That the American Academy of Pediatrics, regarding the provisions for maternal and child welfare, favors the use of public funds to provide *such services to those groups of the population unable to pay for medical services*, to the end that the standards of medical care may be maintained at a high level among such groups.

The Academy of Pediatrics does not favor the use of Federal funds for those able to provide good medical care from their own resources.

The Academy directs the attention of those considering proposed legislation to its fact-finding study of child health services now in progress which, at its conclusion, should assist in the development of sound programs at state levels based on demonstrated needs.

Pending the completion of this study, it is recognized that urgent needs exist in some states that should be met in the immediate future. To this end, the Academy recommends that additional Federal Funds be made available for grants-in-aid to states under existing maternal and child health and crippled children's programs of Title V of the Social Security Act as amended in 1939.

The Academy would welcome the privilege of sending Representatives now or at any time to confer with those responsible for the preparation of legislation pertaining to child health.

The House of Delegates of the American Medical Association at its December meeting adopted a resolution proposing the formation of a Health Congress, although of rather limited scope, to consist of representatives of the medical, dental, hospital, nursing, pharmaceutical and allied professions, and that it approves the creation of such a coordinating body.

The functions of this proposed Congress are also limited "to undertake to bring to all the people of this nation the complete benefits of modern medical-dental science and the finest hospital facilities, to arrange for budgeting the cost of such services at monthly rates within the financial means of all Americans through voluntary, nonprofit health plans and to work speedily for the institution of such voluntary nonprofit health plans in those places or localities where they do not exist now."

In a similar but much wider vein, the Michigan Medical Society proposes a National Health Conference, with a membership made up of a representative or representatives of each state hospital association, state medical association, state nursing association, state pharmaceutical association, the industry of each state, the labor of each state, the agriculture of each state, a representative of the United States Senate, the House of Representatives, and the United States Public Health Service.

At the meeting in December of the House of Delegates of the American Medical Association, the New Jersey delegation presented resolutions on a Permanent Conference on Medical Care "to be created immediately either by (1) the American Medical Association, (2) the Congress of the United States, or (3) the President of the United States, to be composed of an equal number of representatives of (1) the American Medical Association and (2) the governmental agencies concerned with health services and that the members of such conference be given equal powers of action to the end that the American people may be provided in our time with the best possible quality, quantity, availability and distribution of medical care by concerted American democratic action with resultant peaceful solution of the medical care problems which concern us all."

Perhaps, somewhere among the proposals named there may be found a magnetic field into which the good elements of all might be drawn so that such a congress of workable size could be brought into being to effect a program of health to which all parties having interest therein may subscribe in the cause of harmony, equity, and ultimate success.



Agriculture, industry, labor, business, and members of professions of education, law, and religion, forming what we call the public, have an inherent interest in health planning. These great groups which eagerly seek the advantages of health are not equipped with a knowledge of medicine nor of medical technics by means of which the desideratum of living in health and well-being may be secured. That's why doctors were born!

It is not unreasonable to assume, therefore, that the guidance of physicians should occupy an important, if not the most important position in national health planning. That they have been denied such an authoritative voice, in past and future planning, is a matter of record.

Some of our elder members may have studied medicine, as I did, from textbooks titled "The Theory and Practice of Medicine." Sociomedical legislation is too frequently based upon the views and aims of politically-minded legislators, of administrators and even of a small group of physicians who may be versed more or less widely in the "theory" but not in the practicalities of the "practice" of medicine, although the latter is the only medium through which medical care can be successfully extended to individuals.

Should we not in child health planning have better teamwork? Might we not learn some helpful lessons in team play from the methods of those who indulge in the national pastime of football?

To succeed, the linesmen should be those of sturdy intelligence, representing agriculture, industry, labor, business, and the like. In the backfield are the two halfbacks of the Public Health Service and the Children's Bureau, with a highly important figure, the Academy of Pediatrics, as quarterback, who calls the signals because he knows the game and the strategy of play. The general practitioner who engages in pediatrics is the alert rear guard in the position of fullback.

"Huddles" should be indulged in frequently in the interest of coordination, upon which the winning of the fray depends. Who are our opponents? They have been well named by the late L. Emmett Holt, Sr., as the forces of "poverty, ignorance and neglect." To conquer them, there is needed the closest teamwork, with a backfield incurring no penalty because it is constantly in motion, but with each and every member of the team spurred with the ambition to quickly reach the goal of success.

Since the writing of the above on Cooperative National Planning for Improving Child Health Services, an encouraging change of mind has been witnessed among the solons of legislation in the Congress who have issued a communique quite in keeping with the intent and purpose of this morning's discussion.

A letter has been addressed to the "leading professional organizations in the field of health and medical care," including our own Academy, actually requesting something unique in the history of governmental health planning, but a proposal equally to be desired and embraced. The letter reads as follows:

#### UNITED STATES SENATE

##### Committee on Education and Labor

There are now pending before the Senate Committee on Education and Labor many legislative proposals as to specific methods of promoting improved health. In considering these proposals, however, it would be a mistake to focus attention entirely upon methods. The time has come, I believe, to ask, "What are our objectives on the nation's health?"

Accordingly, on behalf of the committee, I am writing to the leading professional organizations in the field of health and medical care to ask that they join in a co-operative attempt to stake out specific health goals for the coming five years. I am sure that your organization will be anxious to cooperate in this endeavor.

The enclosed outline sets forth a comprehensive framework for a statement of America's health goals. Some groups will feel qualified to suggest goals for every item; in fact even to add subjects not referred to in the list. Others will want to

confine themselves to specific subjects within their field of experience and competence. Still others will prefer, in some instances, to set forth their goals in terms not only of a five-year period, but also for a ten-year period—in order to indicate the progress that can be made over a longer span of time.

It is obvious, of course, that setting quantitative goals—such as reducing the incidence of a given disease by 50 per cent or raising the number of dentists from 70,000 to a higher figure—does not imply a forecast or prediction of what will actually happen. Setting a goal merely indicates what we should aim at and what we can achieve if we fully mobilize our health resources and take full advantage of the rapid progress that is being made in the arts of prevention, diagnosis and care.

If your organization is presenting a statement to the Committee on the National Health Bill, S. 1606, hearings on which will be held during April, your suggestions for health goals might well be presented at the same time. In any case, the Committee's work on this matter would be greatly facilitated if we could hear from you by the end of April. If this provides insufficient time for final judgment, let me assure you that your preliminary and tentative estimates will nevertheless be greatly appreciated.

I should like to reiterate that this survey is limited to a discussion of goals and does not involve any questions as to alternative methods of achieving a specific goal.

Finally, let me express my confidence that the entire health profession will enthusiastically join in this endeavor and produce a set of health goals fully consistent with the hopes and aims of our American democracy.

Sincerely yours,

JAMES E. MURRAY

Chairman

Education and Labor Committee

#### Questions on

#### *Health Goals for America's Future*

1. Over the next 5 years, what should be our goals on the nation's health?
  - What should our aims be with respect to increasing the average expectation of life?
    - What should our aims be in reducing—
      - a. the infant mortality rate?
      - b. the maternal mortality rate?
      - c. the death rate at various ages?
    - What should our aims be in preventing or controlling—
      - a. heart disease?
      - b. cerebral paralysis?
      - c. cancer?
      - d. tuberculosis?
      - e. diabetes?
      - f. pneumonia?
      - g. poliomyelitis?
      - h. rheumatism and arthritis?
      - i. rheumatic fever?
      - j. venereal disease?
      - k. malaria?
      - l. dental defects?
      - m. defects of vision?
      - n. defects of hearing?
      - o. mental ill health?

2. Over the next five years, what should be our goals on health personnel, facilities and education?

What should our aims be with respect to the number and distribution of qualified—

- a. doctors?
- b. dentists?
- c. nurses?

What should our aims be with respect to the number and distribution of adequate—

- a. hospitals and hospital beds?
- b. health clinics and health centers?
- c. sanitation facilities?

What should be our aims be with respect to—

- a. medical research?
- b. professional medical educational?
- c. health education for the public?

Although the letter asks for "suggestions for health goals," it also contains a rather disquieting reservation to the effect that "this survey is limited to the discussion of goals and does not involve any questions as to alternative methods of achieving a specific goal," a statement which physicians would view as resembling diagnosis alone, without its desirable companion of indicated treatment.

This letter appears over the signature of the Honorable James E. Murray, Chairman of the Senate Committee on Education and Labor, who is in charge of the hearings now in progress on S. 1606, which bears his name as a cosponsor, the Wagner-Murray-Dingell Bill.

#### DISCUSSION

**CHAIRMAN WALL.**—We regret that time is not available to have discussion from the floor, but we thought perhaps that the panel members might wish to discuss some points among them. We have just heard that Dr. Van Horn wants to ask a question. We will ask Dr. Van Horn to state his question.

**DR. VAN HORN.**—I would like to give one bit of information and also ask a question of Dr. Bauer. You will recall that Dr. Wall has made some reference to the action taken by the Academy at the Detroit meeting, with reference to certain recommendations in seeking additional funds, under the provisions of the Social Security Act. That has been explored with the Congress, and we have been informed that the act will be open, and that we will be given an opportunity for a hearing in order to obtain additional Federal funds under the present provisions of the Social Security Act, to provide for extension of the maternal and child health and crippled children's program.

There is a question I would like to direct to Dr. Bauer, if I may. In one of the stands of the National Health Program of the American Medical Association, I believe it is under Item 2, Dr. Bauer, reference is made, that the Health Department should not assume the care of the sick as a function. What I would like to ask is, does this mean that health departments which administer medical care programs, such as tuberculosis control, venereal disease control, services for crippled children and children with rheumatic fever and heart diseases, should they abandon such programs?

**DR. BAUER.**—The provision in that particular item of the program, Dr. Van Horn, related to medical care in general. I think tuberculosis, venereal disease, and some of the other things you mention are more or less, we may say, taken out of the general medical care program, and it was not related to them.

If I may, Dr. Wall, while I am on my feet, there are one or two remarks I would like to make with reference to some of the other things that were said. Dr. Coffey said that the organized medical profession had given lip service only to the extension of public health services. I think that is not quite an accurate statement. The American Medical Association

has urgently fostered the extension of public health services for years. It has been part of every program of which I have knowledge for a good many years.

In fact, if he looks back in the history of the United States Public Health Service itself, he will find the United States Public Health Service was sponsored by the American Medical Association.

I can cite an instance in my own county. We had no full-time health department in Nassau County, L. I., until, I think it is approximately seven or eight years—it may be ten. We would now still have no health department in Nassau County if it had not been for the Nassau County Medical Society. That society was directly responsible for the establishment of a full-time health department in Nassau County, and one which is, I may say, as well administered and free from political control as any health department anyone can mention.

We had the same trouble about a hospital for the indigent in Nassau County. We had only one indigent ward in the county hospital, and for nearly fifteen or eighteen years, the county medical society urged the establishment of such a hospital and met with nothing but opposition from the political authorities, as they did in the case of the health department, and finally the county society went to bat on it and insisted it be taken through a referendum vote of the population, and they voted for it and we got it.

These are two instances which serve as illustrations.

I will admit there are some county societies that are not very active, and one of the items to which I did not pay any attention in my discussion before is that the A. M. A. is urging a reactivation of these county societies to make a living force for progress in their communities.

One other item I neglected to mention in connection with the national conferences, there has just been held a conference on rural health, a national conference on rural health, by the A. M. A., just this last Friday and Saturday in Chicago, so I have not yet heard the results of it, but we have a very active committee on rural health and as you know, the rural health problem is one of the most important ones which we have, and that committee, which is under the leadership of Dr. Crockett, of Indiana, made tremendous strides in solving the problems of rural health, and they are getting cooperation and active cooperation of the various farm organizations, in helping solve it.

Dr. Van Horn, I think it was, who said we need intelligent, cooperative national planning. I second that most heartily. The only way we can get it is for everyone to sit down as we have here today and listen to the other fellow's viewpoint, and then let us argue in a friendly fashion, and if we think the other man is wrong, let us try to show him where he is wrong. If we are wrong, let us be willing to hear the other man's side of it, and see if perhaps we cannot get together—at least in ninety per cent of our aims.

We all want the same thing. It is a question of how we are going to obtain it. My feeling is that compulsory insurance bills, exemplified particularly in the Wagner-Murray-Dingell Bill, do not represent ideal cooperative planning. I do not think it is particularly ideal, and I am most certain it is not cooperative. It reminds me of when I was about fifteen; I belonged to a club. We were organized for a year. Another group organized a club and adopted our name. We did not like that much. We had a group from each club get together to see if we could not iron it out. We called attention to the fact that we had had the name longer than they had. Their reply was, "We'll compromise. We'll keep the name, and you can take any name you want."

CHAIRMAN WALL.—We'll ask Dr. Coffey if he cares to make an answer to the question.

DR. COFFEY.—Thank you. I am glad Dr. Bauer brought up that specific situation that I pointed to. True it is, medical societies have had a part in organizing health services. I think it only emphasizes my point, that if organized medicine wholeheartedly and actively got behind the development of full-time health services, we would have full-time health services throughout the nation. We would have them today if in the past they had gotten behind them, because the communities will accept the leadership of the medical profession, thank goodness, and by accepting that leadership, they will follow their recommendations.

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But I could not have been in public health administration work for twenty-two years, have worked in every section of the country and have been working toward the development of local full-time health departments without recognizing, without making comment upon the fact that it is because of the lack of action on the part of the medical societies that we do not have one hundred per cent coverage of full-time health services. Too often the position that is taken by the medical societies is, "It is only a step toward socialized medicine." Some place we must draw the line between what is public health and what is socialized medicine, and certainly, in a democracy we must accept—or in any government, for that matter—the responsibility of the government for protecting the health of the people.

Now, I would like to ask Dr. Bauer a question—it is somewhat pertinent to the one Dr. Van Horn brought up. The suggestion was that health departments should not engage in the practice of rendering medical care to individuals. Some place in the A. M. A. program, it does provide for official funds to be used in defraying the expenses of the indigent person. Now, I would like to ask Dr. Bauer what agency of the government should administer those funds, recognizing that if government funds are used, surely some governmental agency would have to be responsible to see that they are expended wisely and effectively.

I am wondering whether Dr. Bauer will tell us that there is any other agency of the government, Federal, state or local, that is better prepared to administer that phase of the program than the health department, recognizing that the health department at least is under the guidance of professional medical men, and at least would be familiar with and recognize the problems at hand.

DR. BAUER.—Medical care to those unable to provide for themselves is best administered by local and private agencies, with the aid of public funds when needed. This program for national health should include the administration of medical care, including hospitalization to all needing it and unable to pay, such care to be provided preferably by a physician of the patient's choice, with funds provided by local agencies, with the assistance of Federal funds when necessary.

Usually, in every community, local organization, either private or maybe public—this refers particularly to Federal administration of medical care, and my own county, we have provisions for caring for the indigent and in this state also there are provisions for the care of the indigent through the Department of Public Welfare of the state, and in this state, the patient does have the right of choice of his own physician. The State Board of Welfare together with the county jointly pay the bill.

DR. COFFEY.—Dr. Bauer said in this state the people, the indigent, are given medical care by the Department of Welfare. I would like to ask specifically, does he recommend welfare departments do such administration of the indigent medical care as is necessary as versus the health department?

DR. BAUER.—I think the care should be administered by the physician. Now, if the care is to be administered by the patient's own physician, I do not think that it makes much difference whether it is the health department or the welfare department that pays for it. I think as far as possible, it should be left on an individual basis.

DR. VAN HORN.—As long as we are all directing questions to Dr. Bauer, I wonder if I may ask another one, Dr. Bauer. A statement is made in the National Health Program that implies a rather sharp distinction between preventive medical services and curative medical services. It is rather difficult, for pediatricians particularly, to understand such a sharp distinction. I think in pediatric practice, one practices one thing one minute and the other thing the next, and there isn't any clear-cut line. I wonder if under the National Health Program, as you visualize it, one agency might be given responsibility for preventive health services, as you have indicated for health departments, and another group will provide the curative services.

DR. BAUER.—I am used to having all these questions thrown at me; it is nothing new. Preventive medical service, I think, covers a lot more than actual preventive medicine through medication. It covers health service, prevention of disease through, as one of these

gentlemen mentioned, the care of the environmental factors, such as sewage disposal, care of the water and milk and food supplies, and mosquito and fly control. That certainly is preventive medicine, but it is something that has to be done by a governmental agency. The individual cannot do that. All these things involve the employment of the police power, and the individual physician does not have police authority. That must come through a governmental agency.

Then, of course, we can go down to the more individual items, such as inoculation against smallpox and diphtheria, and so on, and there again the material should be available through the state health department for individual physicians to give, and if there is no arrangement by which that can be done, as in the case of the indigent, I think the health department would have to make arrangements to give it.

I do not think that it necessarily involves curative medicine in taking care of any of those particular items.

CHAIRMAN WALL.—Any questions on the other side?

DR. NICHOLS.—I have one question to ask Dr. Van Horn on this cooperative story, and I would like to quote, before I ask him the question, for his information, from the Catholic University Book, "Better Times." It says this: "Lasting social reforms can only be accomplished through voluntary cooperation. As a consequence, the state should stimulate its citizens to find a solution of their own problems through free cooperation, and not under any compulsion. A democracy loses its soul when it loses faith in itself and becomes impatient of the democratic progress."

I would like to ask Dr. Van Horn, in accordance with our Academy resolution at Detroit, which favors the use of public funds to provide child health service to those families unable to properly provide good medical care from their own resources, should we not now jointly, Academy, A. M. A., Public Health Service, and Children's Bureau, select this area of agreement that we are all agreed upon and study and promote at state level, and later national level, operating plans, such as the Maryland State Medical Plan, the Newark, New Jersey, Medical Plan, which is now providing good medical care for this group unable to provide this service from their own resources, and study similar plans?

DR. VAN HORN.—I certainly think we should all get together and discuss the problem. I think, of course, it is really the most important problem, the most controversial one in the whole question of providing medical care—that is, the determination of the means test.

There are many people in this country who feel in any medical care program there should be no provision for a means test. I think I can say that as a representative of the Children's Bureau, we certainly would frown upon the idea of subjecting every individual to a searching question as to their financial ability to meet any cost of medical care. I think that that is something that would have to be ironed out, and I don't know as we could come to any agreement on it today, Dr. Nichols, but certainly, I am in hearty accord with the idea of all getting together and sitting down and working out something that is practicable and workable, and that we all agree on.

CHAIRMAN WALL.—I am afraid that time will not permit further discussion, inter-panel discussion, but I want all the members in the audience to realize they have the right to buttonhole the members of this panel as they go out and ask any questions they want to.

I want to thank, on behalf of the Academy, those who have consented to take part in this discussion.



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I do not think that it necessarily involves curative medicine in taking care of any of those particular items.

CHAIRMAN WALL.—Any questions on the other side?

DR. NICHOLS.—I have one question to ask Dr. Van Horn on this cooperative story, and I would like to quote, before I ask him the question, for his information, from the Catholic University Book, "Better Times." It says this: "Lasting social reforms can only be accomplished through voluntary cooperation. As a consequence, the state should stimulate its citizens to find a solution of their own problems through free cooperation, and not under any compulsion. A democracy loses its soul when it loses faith in itself and becomes impatient of the democratic progress."

I would like to ask Dr. Van Horn, in accordance with our Academy resolution at Detroit, which favors the use of public funds to provide child health service to those families unable to properly provide good medical care from their own resources, should we not now jointly, Academy, A. M. A., Public Health Service, and Children's Bureau, select this area of agreement that we are all agreed upon and study and promote at state level, and later national level, operating plans, such as the Maryland State Medical Plan, the Newark, New Jersey, Medical Plan, which is now providing good medical care for this group unable to provide this service from their own resources, and study similar plans?

DR. VAN HORN.—I certainly think we should all get together and discuss the problem. I think, of course, it is really the most important problem, the most controversial one in the whole question of providing medical care—that is, the determination of the means test.

There are many people in this country who feel in any medical care program there should be no provision for a means test. I think I can say that as a representative of the Children's Bureau, we certainly would frown upon the idea of subjecting every individual to a searching question as to their financial ability to meet any cost of medical care. I think that that is something that would have to be ironed out, and I don't know as we could come to any agreement on it today, Dr. Nichols, but certainly, I am in hearty accord with the idea of all getting together and sitting down and working out something that is practicable and workable, and that we all agree on.

CHAIRMAN WALL.—I am afraid that time will not permit further discussion, inter-panel discussion, but I want all the members in the audience to realize they have the right to buttonhole the members of this panel as they go out and ask any questions they want to.

I want to thank, on behalf of the Academy, those who have consented to take part in this discussion.

# The Academy Study of Child Health Services

The rapid growth which the Study of Child Health Services has undergone in the last few months is best illustrated by the contrast shown in the two progress maps for April and July included below. The marked decrease in "white space" in the July map is proof of the zeal and effort with which the state chairmen, executive secretaries, and their associates have carried out the numerous details of the study.

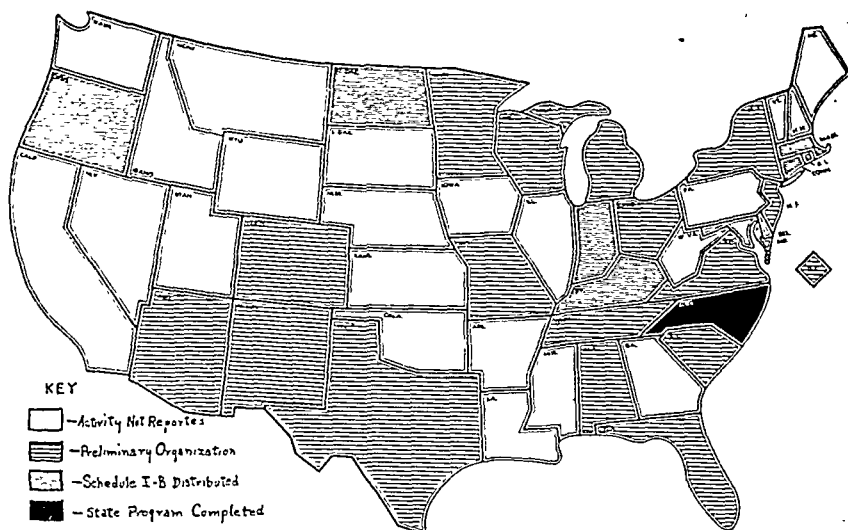


Fig. 1.—April, 1946.

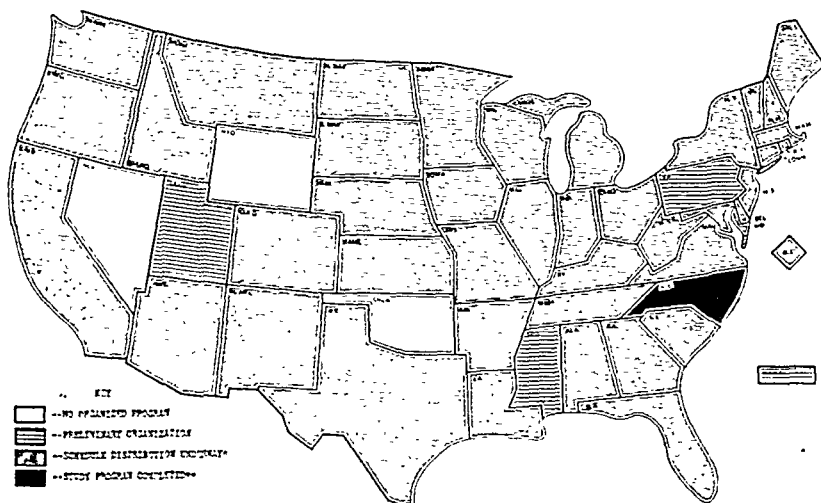


Fig. 2.—July, 1946.

## SCHEDULE DISTRIBUTION

With the preliminary details of organization completed, the arduous process of schedule distribution has begun in the majority of states. Twenty-three states report the distribution of one or more schedules as of June 15. Of the three series of schedules in use, Series I—concerning hospitals and related institutions—involves certain variations of distribution depending on the progress of the Commission on Hospital Care Program. Wherever possible, the Academy Study has been correlated with that of the Hospital Commission. Through the cooperation of the Commission, information on general and pediatric hospitals is being collected in nineteen States. By reason of the difference in timing of the two studies, a special form (schedule I-A) is being used in twenty-eight States not covered by the Hospital Commission. In three States information is being collected by both the State Study program and the Hospital Commission. The remaining schedules of series I on special hospitals have been distributed in fourteen States.

Collection of data pertaining to public and private health organizations (series II) is now under way in thirteen States, with eight States reporting complete distribution of these schedules as of June 15.

Questionnaires for pediatricians, general practitioners, and dentists (series III) have been sent out in nineteen states, and all professional personnel in private practice have been reached in eight of these states.

Preliminary reports of returns of the completed questionnaire are most encouraging. Fourteen states have received completed schedules, and one executive secretary reports that his records show a 90 per cent return from the pediatricians of his state and a 66 per cent return from the general practitioners to date. Since the percentage returns of the completed questionnaires represent the most important part of the study, it is to be hoped that subsequent records will show even greater cooperation on the part of those being asked to supply the necessary information.

## PERSONNEL

Exclusive of committee members and clerical assistants in the state offices, 131 persons are now actively engaged in the conduct of the Study of Child Health Services. This figure includes 56 state chairmen, 1 regional director, 51 state directors, executive secretaries and assistants, and 23 staff members in the Central Office. As of July 1, only six states and the Territory of Hawaii have been unable to secure executive secretaries. It is of interest to note that of the total 49 executive secretaries and assistants, 31 are physicians, of whom 20 are pediatricians; 2 are senior medical students, and the remaining 16 represent a variety of backgrounds including social work, nursing, business, Red Cross, and health and welfare activities.

## SPECIAL FALL MEETINGS

In anticipation of the final stages of the Study when tabular information is to be returned to the states for future study and planning, a special series of regional meeting is now under consideration. In order to "sound out" the opinions of those most closely connected with the individual state programs, the following letter has been sent out to all state chairmen and executive secretaries for the purpose of determining their reactions to the proposed schedule of activities:

June 25, 1946

*Important*

Despite the fact that you have been deluged with material from our office, I sincerely hope that you will give this letter your earnest and prompt consideration.

When our Study was first developed it was intended that the material gathered throughout the States should be presented in an over-all factual report from our Central Office. This will, of course, be done, but it has become increasingly apparent that a report from our Central Office is only a part of the job and that of equal, or perhaps greater, importance is the need for a report to be made at the State level.

To provide the basic data upon which these State reports may be made, we have promised to return to State groups tabular material for each State broken down to the level of counties and cities of 10,000 or more population. There has been considerable discussion in our office of the amount and nature of the material which should be returned to the States and the extent to which this material should be accompanied by a descriptive text. In other words, should we return to the States merely the tabulated material, or should we attempt to outline the type of report that might be written? I feel sure that the answers to these important questions will vary in different parts of the country and that the State Chairmen and the Executive Secretaries who are actually involved in the conduct of the State programs are the ones best qualified to give the answers.

Meetings have therefore been planned in order to allow opportunity for full discussion of this question between those who have been active in the Study at the State level and members of the Central Executive Staff. We are anxious that these meetings should be held at as early a date as can suitably be arranged. However, with summer holidays now approaching it is unlikely that satisfactory meetings could be held before the Fall. For several reasons it appears undesirable to let this matter wait until the meeting of the Academy in November. By November it will have been necessary to crystallize some of the procedures for the analyses and State tabulations. Also, it is likely that in the early Fall several of our Executive Secretaries will have completed their work and be leaving.

In order that the Central Staff may have an opportunity to obtain the opinions of all those who have been conducting the Study throughout the States, it is planned to have three Regional Meetings rather than one over-all meeting. These Regional Meetings do not adhere to the Regional Divisions of the Academy but have been arranged from the point of view of approximately equal division of the country and geographical convenience.

A meeting has been planned in Chicago, at the Palmer House, on September 13 and 14, to include the following nineteen States:

North Dakota	Iowa	Michigan
South Dakota	Missouri	Indiana
Nebraska	Arkansas	Ohio
Kansas	Louisiana	Kentucky
Oklahoma	Wisconsin	Tennessee
Minnesota	Illinois	Mississippi
		Alabama

A meeting has been planned in San Francisco (hotel not yet confirmed), on September 17 and 18, to include the following 12 States and the Territory of Hawaii:

Washington	Nevada	Arizona
Oregon	Montana	New Mexico
California	Wyoming	Colorado
Idaho	Utah	Texas

A third meeting has been planned for September 30 and October 1 at the Mayflower Hotel, Washington, D. C., to include the following 17 States and the District of Columbia:

Maine	New York	Virginia
New Hampshire	New Jersey	North Carolina
Vermont	Pennsylvania	South Carolina
Massachusetts	Delaware	Georgia
Rhode Island	Maryland	Florida
Connecticut	West Virginia	

In order that we may further develop our plans for these meetings, I will appreciate hearing from you as soon as possible whether or not you can attend. Also I shall appreciate receiving any thoughts you may have on the type of discussion which is desired. One suggestion which has been made is that State Chairmen and Executive Secretaries should meet with representative persons or groups from the State Medical Societies, State Health Departments, and their own Advisory Committees prior to these meetings in order to be able to represent as fully as possible the opinions and attitudes of all those concerned in the Study.

The expenses of State Chairmen and Executive Secretaries for attending these meetings should be met from the State Budgets.

Sincerely yours,

JOHN P. HUBBARD, M.D.

## The Social Aspects of Medicine

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Several months ago the following three questions were sent to fifteen members of the Academy representing various opinions in their social thinking.

1. If Federal funds are made available to expand health services and medical care for children, how should they be administered by the Federal agency, by the states and localities?

2. What should be the composition and function of an advisory committee to each type of agency?

3. Should technical advisory committees be separated from general advisory committees that include representatives of the public and the professions?

Nine replied. The answers are as follows—

Dear Dr. Park:

In answer to your questions I should say—

1. a. Federally, probably through the Children's Bureau.

b. By the states, through the medical schools, or where none available, or it is not desirable, through the State Board of Health.

c. By the localities, through the local society in co-ordination with the county health bureau.

2. It seems to me that too many cooks will spoil the soup. The responsibility should be chiefly invested in each state, with something of a competitive spirit and due credit given for progress shown. The committee should be purely advisory and should be composed of Academy members only. Each state Pediatric Society should elect their advisory committee on this work.

3. I do not thoroughly understand this question. I have always felt that it is wise to include the public in committees that are getting health work done. A great deal of stimulation and aid in actual work can be secured in this manner.

I would appreciate any further information that you have under question 3, and look forward with great interest to how your analysis of the reports on these questions turns out.

Sincerely yours,

H. F. GARRISON, JR., M.D.

Jackson, Mississippi.

Dear Dr. Park:

In answer to your questions I should say—

1. If Federal funds are made available to expand health services and medical care for children, the Federal agency to administer the funds, in my opinion, is the Children's Bureau. In Wyoming I served two years as director of maternal and child health and of crippled children. The agency, at the State level, to administer the funds should be the Health Department. This could be much improved in our State, and doubtless in the future will be improved. Locally, the county health officers should administer the funds, though at first, in the counties where there are inadequate health officers, this will not be satisfactory.

2. The advisory committee should be made up of representatives of organizations which have the welfare of children at heart: P. T. A., schools, women's clubs, American Association of University Women, American Legion, ministers, doctors, and dentists.

The function of the committee should be the initiation of reforms, and the support of programs such as the immunization of preschool children, the proper examination of school children with particular attention to problems of nutrition, dentistry, hearing and visual

defects, good posture including good feet, the detection of hernias, and their repair, and mental hygiene. I was on the board of doctors who helped in the induction of men into the Armed Services, and I was depressed by the number of hernias which should have been detected years before. The community in general should be represented, for as it is now, the doctors and dentists are afraid that their incomes will be cut down and discourage anything which seems to threaten their practices. This is natural, but I think it would be reassuring for the doctors to confer with men and women who see the problem from the point of view of the public at large, which includes poor people who are not receiving adequate care.

3. The advisory committee should have representatives from both the people and the professions, with provision for regular meetings of the groups, together and separately.

Sincerely,

PAUL W. EMERSON, M.D.

Cheyenne, Wyoming.

Dear Dr. Park:

It would seem to me that your first question could hardly be answered in the negative, since with state and local administration a more sensitive machinery is employed. In this way the local needs are more closely met and any criticism is more easily applied to responsible authorities. It seems to me that the criticism felt toward the Children's Bureau is due to its remote control and its inability to establish a general plan that suits individual conditions.

Your second question is more difficult but I would think that the executive secretaries of the various child caring agencies would form the basis of such a committee with interested pediatricians.

I see no reason for a separation of the technical advisory committee being made; they could, of course, have their meetings, if necessary, and report to the general board for discussion.

We have so much confidence in the ability and sincerity of our State and local Boards of Health that we would be much more cooperative with their efforts than with a Federal agency.

With kindest regards, I am,

Birmingham, Alabama.

Sincerely yours,

CLIFFORD L. LAMAR, M.D.

Dear Dr. Park:

I apologize for my delay in answering questions submitted by you some time ago. In answer to question 1, I would favor the over-all policy-making by the Federal administration and the actual operation carried out by the state and localities.

I would think that the advisory committees should be composed of both lay and medical men with professional domination. A representative of the United States Public Health Service and Children's Bureau might well be included.

The technical advisory committee should be separated from the general advisory committee due to their special knowledge and the fact that they would be responsible for the functioning of the organization.

I favor, along with most medical men, a creation of a Cabinet post of health in Washington which, it seems to me, would simplify the correlation of government and private medical care.

I have enjoyed the discussion by you in the recent issues of the JOURNAL OF PEDIATRICS and believe some definite good will be derived from them.

Very sincerely yours,

JOE T. SMITH, M.D.

Knoxville, Tennessee.



My dear Dr. Park:

This is an attempt to answer your questions, but the point of view may obscure the attempt somewhat.

It is my opinion that the time is at hand, or should be shortly, for representatives from the three major health agencies dealing with children, namely, private pediatricians, Public Health services, and the Children's Bureau, to sit down in conference and define the spheres of influence of these agencies. At the periphery of these spheres there will be overlapping problems, new and old. To act upon these problems, there should be a standing technical committee consisting of professional people from each group.

There are health problems best handled at a local level, others at a state level, and still others at a national level, and the funds allocated should be administered by the agency at which level the problem is handled. To illustrate: the problem of the migrant workers who travel from state to state must be solved primarily at a national level, although assignments for administering the care may be made to states and localities. The problem of poliomyelitis, at present on a county level, could be handled better on a state or semistate level. Sparsely populated counties cannot set up and maintain the best modern facilities for its care; it is neither economical nor desirable that they should. Poliomyelitis also illustrates the desirability of defining and delegating problems to the right agency. The Poliomyelitis Fund, a separate and unique fund, has invaded the field covered by the Crippled Children's Act. Questions arise, such as, "Shall children crippled with poliomyelitis and now carried by Crippled Children's funds, be reassigned to poliomyelitis funds?" Poliomyelitis is a reportable disease; shall cases in the acute stage be transferred over county lines? The Poliomyelitis Fund is designed to meet the needs of any individual suffering from the disease; what then becomes the status of the private doctor in relation to the patient? He is not generally paid by the Fund. This disease alone, therefore, brings up questions involving the Children's Bureau, Public Health, and the private physician, and none of these questions has been answered. There is at present no machinery (Technical Committee) to turn these questions over to for solution or recommendation.

Advisory committees should be separate groups concerned not with the "who" but with the "how" of giving the aid to the right children at the right time and in the best possible manner. These committees should consist of representatives from professional and lay organizations of the community which they serve.

Sincerely,

H. E. THELANDER, M.D.

San Francisco, California.

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Dear Dr. Park:

1. *Administration of Federal Funds.*—This is the most difficult of the three questions to answer. The expenditure of public funds at any level necessarily should and does require a strict accounting. I can recall, in my limited experience, no occasion when the politicians' cry of "graft" has arisen in reference to the use of funds for medical purposes. Inevitably, of course, it will, and then such accounting will be the profession's shield and mainstay. Unfortunately, on a Federal level, this accounting requires an amount of "red tape" so cumbersome as actually to interfere, in my opinion, with the efficient administration of a medical program.

I see very little wrong with the present system whereby the several states are allocated funds through the Children's Bureau and account for them through already established administrative channels. The greatest fault I can think of is the tendency of the Bureau to use the "withholding of funds until . . ." mechanism as a club to force state cooperation, an expedient practice but not one calculated to inspire love and affection essential to real, rather than apparent, cooperative endeavor.

The dispersal of funds within the states is the point at which the greatest finesse and administrative skill are required to operate any health or medical program effectively. Probably, elimination of local subdivision and the establishment of administration directly from the state to the individual is the most easily workable plan but this will, of course, vary in different states.

I think that the crux of the matter lies (as always) in the person selected as administrator at the state level. In conducting a health and medical program dealing with children, the state director should be a pediatrician. Furthermore, he should be a pediatrician of the first rank whose skill and judgment command the respect of his fellows. He should also have administrative skill, although I think that experience in administration is perhaps overweighted as a requirement by many Public Health workers today. Such a person is, admittedly, a rare bird. For this reason, he is probably not to be had for the remuneration usually available for medical public officials. In short, a man good enough for the job should be paid at least as much as he might expect to make in private practice or other positions in the field of Pediatrics. This concept will prove a stumbling block almost everywhere, even if funds are available to provide a suitable salary, because of the prevalent low salaries in other medical fields of public service and the inevitable jealousies and squabbles which would follow the creation of a position out of line with similar jobs in the same government. The selection of a capable and strong-minded state administrator would automatically go far toward alleviating the present much-deplored tendency of the Children's Bureau to carry policies and procedures past the state level, their proper end point.

This brings us to the matter of the proper agency from which to administer these funds. So far as the Federal level is concerned, I am in accord with those who believe that all medical and health affairs should be executed by a single agency. Whether such an agency has Cabinet, Bureau, or other status is a matter for the political economists to decide. I think it is impractical to consider administration at the state level by other than the regularly constituted existing health agency. If it is felt that this agency is incapable, steps should be taken to make it effective since I do not feel that the health of children can be completely "compartmentalized" and divorced from the considerations of the general welfare of the people of a state. It is entirely feasible, on the other hand, to alter existing administrative techniques to encompass the enlarged responsibility implied in any such program. One such alteration may and should be the creation of (or the strengthening of one already existing) an advisory committee for the children's program.

2 and 3.—*Advisory Committees.*—First of all, advisory committees, at whatever level, should function. In order to function, I think that a committee should be small in numbers, wide in representation, and superior in composition. This is a roundabout way of indicating that the personality, character, intelligence, and special capabilities of the individual members are paramount. If this is neglected committees will either be impotent or dominated by one or two individuals.

The Federal Agency is, I believe, best served by at least two advisory committees. Foremost should be a committee functioning much as does a Board of Health or the Board of Directors of a Hospital. In determining the composition of this committee, selection might be based on eminence and ability in pertinent special fields as well as general character. If such a national committee included representatives of Pediatrics, Social Service to Children, Finance, Government, Economics, and Public Health, it might be reasonable to utilize individual committee members as consultants on special problems as well as submitting over-all policies to the committee as a whole. A second Federal level committee should be purely technical and obviously composed of pediatricians. Even though our pediatric organizations, such as the Academy, have no official status (and this fact should never be forgotten) it is entirely reasonable to depend largely if not entirely upon them to determine the makeup of this technical committee. So far as technical advice from allied fields, such as nursing, dentistry, education, etc., I believe that the liberal use of individual consultants rather than committees is the more effective procedure.

At the state level, one committee, analogous but not necessarily exactly parallel in composition to the National Advisory Committee on policy, should suffice. Its precise composition in each state must depend upon: (1) the nature of the problems peculiar to that state, and (2) the material available for selection. For technical advice, the State Director should rely upon the body best qualified to solve the particular problem at hand and, if he is to be an effective administrator, he should be allowed a maximum freedom of choice. Many problems have satisfactorily ready-made solutions already determined at the Federal level and for those of a purely local nature the advice of the Pediatric representatives on his central committee might reasonably be sought.

In summary I should like to reiterate that the success of any program of child health and medical care hinges, in my opinion, upon the securing of capable administrators at all levels but especially at the state level.

GLIDDEN L. BROOKS, M.D.

Lewiston, Maine.

Dear Dr. Park:

Before answering the questions that you asked me, I think my attitude toward the subject of government aid in medical care, which is presupposed by your questions, should be given. I am convinced that government should shoulder part and in some instances the whole of the expenses incurred by many families in the event of illness. The mechanism whereby this can be done and still have the family retain not only its own self-respect but a respect for the medical profession is difficult, but, I think, possible. It should be done with the approval of a great majority of physicians. This also is difficult, but, I believe, possible.

The indigent should be able to consult the physician of their own choice and the physician render the bill to the government. If a family has an income inadequate to pay extraordinary medical expenses, the government should aid them, but they themselves should bear some of the expense. If, however, they are in moderate or well-to-do economic circumstances, the government should be asked to aid them little, if any. It would not be difficult to state definitely who is in each group. How much income a family receives is an open book to the government and any family could obtain a card or some other identifying means to enable a physician to know whether they are to be fully or partially taken care of by the government. The expenses of such an undertaking would be minimal as compared with the all-inclusive health program proposed in the present legislation. Not only would this be less expensive, but it would preserve the personal contact with patients that the medical profession has always regarded, and rightly, with jealousy.

We are now seeing a group of children who have been taken care of at government expense during the first year of their lives. These children for the most part are from couples in the low-income group. Most of them would not have come to a specialist during this period had not the government paid their expenses. Now that the year is up, a large group of them are continuing to come to my office because, in my opinion, they have discovered that there is a value in being taken care of by a children's specialist. They have spread this feeling among their acquaintances in no way connected with the government's bounty and they have brought their children in for routine care. So rather than decreasing my regular fee-for-service practice, it has actually increased the group of those who seek my services.

In 1937, Dr. L. R. DeBuys\* in his Presidential Address to the Academy summarized, from a questionnaire which he had sent to pediatricians, what he considered to be the future of Pediatrics. He did not paint a very reassuring future for our profession. However, since that address almost every mother has come to know what a pediatrician is and what is his value. I think this is in no small measure due to the fact that the government by means of the EMIC program has made "pediatrician" a word familiar to every mother, rich or poor. We have never been so busy as we are now. If we are as valuable as we think we are, this is a good thing not only for our profession, but for better care for children.

\*DeBuys, L. R.: *Whither, J. Pediat.* 11: 409, 1937.

If there is no economic barrier to the use of a pediatrician, then there must be more of them, and they should be good. This is a problem adequately analyzed by Dr. Wilson\* in a recent letter to the JOURNAL OF PEDIATRICS and to which I wholeheartedly subscribe. It can be solved, as he states, only by better and more pediatric instruction in medical schools and in hospitals. I am, however, convinced that medical education should be handled in the same way as medical care. If a candidate can demonstrate his ability to be a good physician, the government should remove all financial barriers. If he or his parents cannot or can only partially pay for his education, then the government should complete the financial requirements. I do not believe that it would be necessary for medical education to be entirely subsidized by the government, but it could be done by some such method as I have indicated for medical care.

The result in the first instance would be that all children whose parents desire it could have the advantage of qualified pediatricians. The result in the second instance would be that all students who would qualify as pediatricians would be educated whether or not they were financially prepared. Such a total program would not be as expensive as the proposed plan. Furthermore, the proposed legislation deals with the medical care of children almost exclusively, as Dr. Wilson points out. It ignores the fact that means must be provided to obtain more and better pediatricians if all children are to have adequate medical supervision.

Federal funds for child care should be given to the state with qualifications that the state use those funds meeting certain definite but broad requirements. These requirements are rightly the prerogative of the Federal agencies, for they are the source of the income. Requirements and restrictions should be arrived at with the approval of an advisory board. On an advisory board to the Federal agencies should be representatives of organized medicine, voluntary medical organizations, medical schools, lay organizations; but there should be a large group of practicing pediatricians who represent those who practice with this the sole qualification for their being on such an advisory body.

The state should disperse these funds to the communities, but also with restrictions. Each state has its peculiar problems and should be best qualified to meet the diversities presented. Federal funds should be given with an appreciation of the state differences. That type of committee which supervises the Federal disbursement of funds should be set up in the state and regulate the allocation of funds to the community.

The ultimate spending of the Federal funds is placed with the locality. What is undertaken here should be the result of a decision by a group similar to that described before. These local projects should have already been reviewed in the Federal and again in the state group. Not only should there be a flow of ideas from the Federal to the state to the community, but there should be a mechanism whereby there would be a similar flow from the community to the state to the Federal group.

You ask if there should be an advisory committee to each type of agency. I have indicated that I think this is essential. You further ask if I believe there should be a general advisory and a technical advisory committee. It seems to me that the end would best be served if there were a general advisory committee which would have on it subcommittees of a technical nature; for example, committees who inquire into the problems of medical education, special graduate education, hospitals, clinics, sanitation, housing, etc.

Sincerely yours,

PAUL W. BEAVEN, M.D.

Rochester, New York.

Dear Dr. Park:

In reply to your letter regarding Federal aid in health services and medical care to children.—

The experience gained in the EMIC program is too valuable to be discarded and any future Federal aid might be based on the framework of this progress. The experience of the Children's Bureau should be utilized for Federal administration. It would seem logical,

\*Wilson, James, L.: J. Pediat. 28: 231, 1946.

however, to have this Bureau function as an advisory and coordinating agency. Broad principles could and should be established by the Federal agency under which state agencies would operate. Certain of the principles should be mandatory; e.g., definition of specialty, minimum hospital standards, etc. Other principles should be advisory in nature. The individual states should have the authority to set up their own methods of administration, fee schedules, and policies. Local authorities should work under state authorities.

The technical advisory committees to both the Federal and state agencies should be made up of practicing physicians, with representatives from the health department and the welfare department. This committee should have liberal and authoritative representation on a general advisory committee which consists of representatives from all recognized agencies interested in child health and welfare.

I would then envision the program thus:

A Federal grant-in-aid to individual states administered by individual states with advisory function and coordination centered in the Children's Bureau; that the setup in the Children's Bureau be the result of cooperation between the executives of the Children's Bureau and a technical advisory committee, with the approval of the general advisory committee. The same plan operating in each state either through the existing maternity and infants department of the state health department or a special agency set up by the state for its administrations.

The present method of local administration of EMIC program through local health departments seems to me the most logical way to handle local claims.

Sincerely yours,

ARTHUR H. LONDON, JR., M.D.

Durham, North Carolina.

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Dear Dr. Park:

1. If Federal funds are made available to expand child health services and medical care, I would feel that the Federal agency should administer them on the basis of actual need for the individual state, or on a matched basis either on equal amounts, or a ratio as high as 3 to 1 dependent upon the financial resources of the state, rather than on the basis of infant and maternal mortality rates. A state might have a fairly low rate but be unable to meet the needs for such a program because of inadequate funds for a well-balanced medical care program. The Federal policy should be general and the regulations for the use of these funds should be made to fit the needs of the individual state. I also feel that the state and community should have some financial responsibility in order that they would have the feeling that they are an actual part of the program, rather than it is just another Federal project.

The funds allotted to the state should be under the administration of the already existing agency the Maternal and Child Health Division of the State Department of Health, rather than setting up a new agency for the handling of these funds. The funds raised at the local level could also be under this same mentioned division and coordinated into the state plan thereby making tax list and monies for health work with children available for state matching. The basis for matching money of these communities would be on their ability to raise money from the tax list and endowments given for health purposes. Communities with small tax lists but with actual needs existing should have a higher ratio for matching such as 3 to 1.

2. The local advisory committee, or "The Health Committee" as it is known in Vermont, should be composed of the selectmen, overseer of poor, health officer, members of the medical and dental professions, representatives of the various religious and fraternal organizations, and the Red Cross. The function of this committee, assisted by the public health nurses, is sponsorship of the program as set up by the state plan. They aid in educating the general public in the aims of the program, give assistance at medical conferences and, most impor-

tant of all, are responsible for getting money from the tax list at town meetings. The success of the program is their responsibility both in the local and state plan.

The state advisory committee should be composed of the leaders in the various state organizations who are interested in the health of the child such as State Medical and Dental Societies, State Department of Education and Welfare, Women's Clubs, State P. T. A., and other welfare organizations. Their function would be to assist the official agency in making general policies and plans for the program. They could be of great aid in obtaining funds from the state government by making known the demands for need for such a program of child health services.

The Federal advisory committee should be composed of professional and lay organizations at the national level, but with state representatives who know the state problems and reactions of the professional groups as they are very varied in the many states. Its function would be to make general policies and recommendations as the needs arise in relation to the health services, and long-range planning adjusted to the needs of the times.

3. The technical advisory committee, the function of which would be to establish medical policies and procedures, could best obtain their objectives if separated from the general committee but they should serve in a dual capacity as part of the general committee in order to obtain the viewpoint of the lay and professional groups.

PAUL D. CLARK, M.D.

Burlington, Vermont.

## Academy News

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On June 22, Dr. Joseph S. Wall, Chairman of the Academy Committee on Legislation, appeared before the Senate Committee on Education and Labor, on behalf of the American Medical Association, which was holding hearings on the Pepper Bill (S. 1318). Dr. Wall submitted a statement which covered in large part the report of his Committee which was published in the JOURNAL last March (J. PEDIAT. 28: 364-372). To this he added the resolutions which were passed at the meeting of the Academy which were published on page 384, and the criticisms of the bill by Dr. Butler, which were approved by the Academy and were published on pages 390-391.

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Dr. Stewart H. Clifford of Brookline, Massachusetts, has accepted the Chairmanship of the Committee on Fetus and Newborn, following the resignation of Dr. Ethel C. Dunham, of Washington, D. C.

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Dr. James G. Hughes of Memphis, Tenn., has accepted the position of Chief Liaison Officer for The American Legion, following the resignation of Dr. Hugh McCulloch of St. Louis, Mo.

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## News and Notes

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Citation with the Bronze Star Medal was received by Lieutenant Harold A. Rosenberg, Waterbury, Conn., of the United States Naval Reserve. The citation was made "For meritorious services in connection with operations against the enemy as a medical officer attached to a Marine air base in the *Ryukyu Islands* area during the period April 5 to June 7, 1945. *Lieutenant Rosenberg*, laboring long hours under extremely adverse weather conditions and in areas which were daily subjected to enemy aerial assaults and shelling, maintained high standards of health and sanitation among the units based at the airfield served by his organization, thereby keeping epidemic diseases to a minimum and preserving the combat efficiency of personnel in the performance of the prodigious tasks which faced them during a particularly critical period of the *Okinawa* campaign. *Lieutenant Rosenberg* also rendered extremely valuable service in the treatment and evacuation of wounded personnel, frequently facing great danger in the performance of such duty. His courageous devotion to duty, tireless efforts and high professional skill contributed materially to the success of the *Okinawa* campaign and were in keeping with the highest traditions of the United States Naval Service."

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The following Fellows of the Academy have been released from the Armed Services:

Dr. John B. Ahouse, Yonkers, N. Y.  
Dr. Alexander J. Alexander, Lexington, Ky.  
Dr. William Thomas Auld, Stockton, Calif.  
Dr. James E. Bowman, Philadelphia, Pa.  
Dr. John Dorsey Craig, New York, N. Y.  
Dr. George L. Drennan, Jacksonville, Ill.  
Dr. Ernest Ekermeier, Tallahassee, Fla.  
Dr. Frederick H. Fehlmann, San Diego, Calif.  
Dr. Banice Feinberg, Providence, R. I.  
Dr. Harry E. Gerner, Jersey City, N. J.

Dr. James B. Gillespie, Urbana, Ill.  
 Dr. A. Lawrence Gleason, Oakland, Calif.  
 Dr. Martin J. Harris, Louisville, Ky.  
 Dr. Howard M. Jacobs, Chicago, Ill.  
 Dr. Samuel Karelitz, New York, N. Y.  
 Dr. Willard Z. Kerman, Chicago, Ill.  
 Dr. Bertrand I. Krehbiel, Topeka, Kan.  
 Dr. William Wayne Lockwood, Spokane, Wash.  
 Dr. Selby V. Love, Louisville, Ky.  
 Dr. R. J. McGillicuddy, Lansing, Mich.  
 Dr. Alvah L. Newcomb, Winnetka, Ill.  
 Dr. Ralph E. Netzley, Pasadena, Calif.  
 Dr. William B. Nevius, East Orange, N. J.  
 Dr. E. Harrison Nickman, Atlantic City, N. J.  
 Dr. Roderick A. Norton, Tacoma, Wash.  
 Dr. Lyon N. Pearlman, Ottawa, Ont., Canada  
 Dr. Allan Ross, Montreal, Que., Canada  
 Dr. Eli Rubens, South Bend, Ind.  
 Dr. Noel G. Shaw, Evanston, Ill.  
 Dr. Matthew M. Steiner, Chicago, Ill.  
 Dr. Benjamin M. Spock, New York, N. Y.  
 Dr. James W. Stirling, Bellevue, Pittsburgh, Pa.  
 Dr. T. Durland Van Orden, New York, N. Y.  
 Dr. Alfred Weller, Arlington, Mass.  
 Dr. Arnold Wideman, Philadelphia, Pa.  
 Dr. A. Alvin Wolf, Chicago, Ill.  
 Dr. Carl Zelson, New York, N. Y.

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The following promotions have been reported to the JOURNAL:

*Army*

Captain Horst A. Agerty to Major.  
 Captain Clinton Hollister to Lieutenant Colonel.  
 First Lieutenant Edward B. Plattner to Captain.  
 Major Irving Rosenbaum, Jr., to Lieutenant Colonel.  
 Captain Thomas E. Shaffer to Major.

*Navy*

Commander Stanley V. Laub to Captain.

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*United States Public Health Service*

Dr. Carl Zelson has been promoted to Surgeon in the United States Public Health Service.

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The American Pediatric Society at its Fifty-sixth Annual Meeting at Skytop, Pa. on May 1 to 3 elected the following officers for 1946-1947:

President:	Dr. Harold K. Faber, San Francisco, Calif.
Vice-President:	Dr. Howard H. Mason, New York, N. Y.
Secretary-Treasurer:	Dr. Henry G. Poncher, 1819 W. Polk St., Chicago, Ill.
Recorder:	Dr. Stewart H. Clifford, Brookline, Mass.
New Member of the Council:	Dr. Joseph Stokes, Jr., Philadelphia, Pa.

The following candidates were elected to active membership of the Society:

Dr. Russell John Blattner, St. Louis, Mo.  
 Dr. Paul Leo Boisvert, New Haven, Conn.



Dr. Charles Alderson Janeway, Boston, Mass.  
 Dr. Herbert Chauncey Miller, Jr., Kansas City, Kan.  
 Dr. Albert Bruce Sabin, Cincinnati, Ohio  
 Dr. Milton J. E. Senn, New York, N. Y.  
 Dr. Helen Brooke Taussig, Baltimore, Md.

The Society also received a sum of \$15,000 from Mead Johnson and Company, Evansville, Ind., to be known as the "Mead Johnson Vitamin A Fund." Grants-in-aid from this fund will be used for research and studies in the field of fat soluble vitamins. A committee consisting of Dr. Edwards A. Park, Dr. Allan M. Butler, and Dr. Daniel C. Darrow was appointed to administer all grants-in-aid in connection with the use of funds. All applications for grants and correspondence should be addressed to Dr. Edwards A. Park, 601 N. Broadway, Baltimore 5, Md.

The new officers of the Society for Pediatric Research elected at the meeting at Skytop, Pa., April 30-May 1 are:

President: Dr. Mitchell I. Rubin, Buffalo, N. Y.

Secretary: Dr. Robert Ward, 477 First Avenue, New York 16, N. Y.

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Dr. Harold O. Ruh, Cleveland, Ohio, died from coronary thrombosis on May 18, 1946, at the age of 62.

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Dr. Murray B. Gordon, New York, N. Y., died June 29, 1946.

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#### MANUSCRIPTS INVITED FOR NORTON MEDICAL AWARD

The book publishing firm of W. W. Norton & Company, Inc., announce that they are again inviting manuscripts for submission to be considered for the Norton Medical Award of \$3,500 offered to encourage the writing of books on medicine and the medical profession for the layman. The first such award was made to *The Doctor's Job*, Dr. Carl Binger's book, published last spring, which gave the doctor's point of view on his work. Announcement will be made shortly of the winning book for 1946. Closing date for submission of manuscripts this year is November 1, 1946. All particulars relating to requirements and terms may be had by addressing W. W. Norton & Company, Inc., 70 Fifth Avenue, New York 11, N. Y.

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#### FEDERAL SECURITY AGENCY

Washington, D. C.

Wednesday, July 17, 1946

With the reorganization of the Federal Security Agency going into effect yesterday, Federal Security Administrator Watson B. Miller today welcomed members of the United States Employees' Compensation Commission, the Children's Bureau and the Division of Vital Statistics, transferred to the Federal Security Agency by Reorganization Plan No. 2, and announced major changes in Agency organization and assignments of duty.

The Federal Security Agency, he stated, will be reconstituted under four main operating branches and six staff offices. The four branches are:

*Social Security Administration*—taking over the old-age and survivors' insurance, employment security, and public assistance programs formerly administered in the Agency by the Social Security Board, which was abolished by the Reorganization Plan, together with activities of the Children's Bureau, transferred from the Department of Labor.

Arthur J. Altmeyer, who has served as Chairman of the Social Security Board since February, 1937, has been appointed Commissioner for Social Security to head this new unit. Miss Katherine Lenroot, Chief of the Children's Bureau since November, 1934, will

continue in that post. No changes in the chiefs of the social security programs are contemplated.

*Education*—consisting of the existing Office of Education. The other educational functions of the Agency relating to the American Printing House for the Blind, Columbia Institution for the Deaf, and Howard University will be under the direction of the Commissioner of Education.

John W. Studebaker, Commissioner of Education since October, 1934, will continue to head this Office.

*Public Health*—consisting of the U. S. Public Health Service. Freedmen's and St. Elizabeth's Hospitals will be under the direction of the Surgeon General. The Division of Vital Statistics, transferred from the Department of Commerce, becomes part of the U. S. Public Health Service.

Thomas Parran, Surgeon General of the Public Health Service since April, 1936, will continue in this capacity. Halbert Dunn will remain as head of the Division of Vital Statistics.

*Office of Special Services*—a new office including the newly created Bureau of Employees' Compensation and the Employees' Compensation Appeals Board which succeed the U. S. Employees' Compensation Commission, abolished by Reorganization Plan No. 2; the Food and Drug Administration; and the Offices of Vocational Rehabilitation, War Property Distribution, and Community War Services.

Mrs. Jewell W. Swofford, Chairman of the U. S. Employees' Compensation Commission since July, 1933, has been appointed to direct this Office as Commissioner for Special Services. Senator Hattie Caraway, formerly a member of the U. S. Employees' Compensation Commission, will serve on the Employees' Compensation Appeals Board, which is established, in accordance with the Reorganization Plan, to hear and decide appeals of employees of the Federal and District of Columbia Governments.

In addition to these 4 operating branches, existing staff offices—Executive Assistant, General Counsel, Research, and Information—have been augmented by two new offices to provide for expanded functions of the Federal Security Agency.

*The Office of Federal-State Relations*—will be responsible to the administrator for study and recommendations in line with Section 10 of the Reorganization Plan. This provision looks toward the coordination of grant-in-aid administration and directs the Federal Security Administrator to establish, insofar as practical, uniform standards and procedures so that State agencies administering 2 or more grant programs may submit a single State plan, and be subject to unified fiscal, personnel, and other policies.

George E. Bigge, member of the Social Security Board since August, 1937, will head this Office.

*The Office of Inter-agency and International Relations*—will be responsible to the Administrator for formulating, establishing, and coordinating the Agency's relationships with other Federal agencies, international agencies, representatives of foreign Governments, and organized groups in the fields of health, education, welfare and social security.

Mrs. Ellen S. Woodward, member of the Social Security Board since December, 1938, will serve as Director of this Office.

With these additions, the Administrator's immediate staff, headed by Assistant Federal Security Administrator Maurice Collins, will remain substantially as at present constituted.

In making public the Agency's new organization, Mr. Miller paid a warm tribute to the units affected by the Reorganization Plan, and expressed his confidence that the changes now in process would not only simplify and improve administration but also promote their common purpose of health, education and security.

Commenting on the relationship of Children's Bureau programs to other services within the Agency, Mr. Miller stressed his concern, and that of the Agency as a whole, for the welfare of children and young people.

"We are very mindful," he said, "of youth's stake in all provisions for health, education and security—and of the Government's obligation to make adequate provisions to the end that all children and young people may get a good start in life. For administrative purposes, the Children's Bureau, with its programs for maternal and child health, child welfare, and crippled children's services, has been placed in the Social Security Administration. But its relationships with both health and education are fully recognized, and effective coordination in this field will be one of our major objectives. Studies will be inaugurated at once and maintained on a continuing basis, looking toward improvements in procedures and the strengthening of relationships.

"We are all," he pointed out, "public servants entrusted with the task of administering laws which Congress has passed in the interests of the general welfare. We have worked together in the past—because our jobs have thrown us together. Reorganization will strengthen the cooperation which we have already built up and open the way to 'combined operations' on a much broader front. As the President pointed out in his Reorganization Message, the further simplification of the Agency's 13 grant-in-aid programs represents a practical step toward improving both Federal and State administration. Since the Plan was made public in May, we have received expressions of warm approval from Governors and other State officials. We know that we can count on their cooperation, as they can on ours.

"We all realize," he continued, "that we have a big job and a big opportunity. We cannot do everything at once. But the path to continuing development has been cleared. We enter into our new relationships in a spirit of joint enterprise, of step-by-step exploration, study and progress in administering the health, education and social security measures with which this Agency is charged. For children, for the aged, for the handicapped, and for the people at large, we shall endeavor to make the most of the improvements now within reach."

When the Federal Security Agency was established by Plan No. 1 under the Reorganization Act of 1939, it brought together the Office of Education, the Public Health Service, the Social Security Board, the United States Employment Service (transferred during the war to the War Manpower Commission, and now in the Department of Labor), the Civilian Conservation Corps and the National Youth Administration (both of which have been terminated). Plan No. 2 under the same Act brought the American Printing House for the Blind into the Agency in 1940, and Plan No. 4 transferred to it the Food and Drug Administration, St. Elizabeth's Hospital, Freedmen's Hospital, Howard University and Columbia Institution for the Deaf. The Office of Vocational Rehabilitation was established in the Agency in 1943 to administer the expanded Federal-State civilian rehabilitation program under the Barden-LaFollette Act. The Office of Community War Services, now in liquidation, was developed during the war to implement the Federal Security Administrator's responsibility for coordinating emergency services in health, education, welfare, recreation, social protection and related fields. The Office of War Property Distribution was set up in 1945 to work with the War Assets Administration in facilitating the distribution of surplus property to health, education, welfare and other non-profit institutions having priorities under Section 13 of the Surplus Property Act.

In addition to transferring the functions of the Employees' Compensation Commission, the Children's Bureau (with the exception of its child labor functions which remain in the Department of Labor), and the Division of Vital Statistics to the Federal Security Agency, abolishing the 3-member Social Security Board, and providing for the coordination of grant-in-aid programs, the present reorganization includes the following changes:

#### Under Plan No. 2—

the functions of Assistant Commissioner of Education are transferred to the Office of Education to be performed under the direction of the Commissioner of Education;

the Federal Board of Vocational Education and the Board of Visitors of St. Elizabeth's Hospital are abolished;

functions with respect to the vending stand program for the blind are transferred from the Office of Education to the Federal Security Administrator; and will be administered under the Office of Vocational Rehabilitation;

Under Plan No. 3—

functions with respect to Army and Navy patients, formerly cared for at St. Elizabeth's Hospital, are transferred respectively to the Secretaries of War and Navy.

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U. S. DEPARTMENT OF LABOR  
WASHINGTON 25, D. C.

July 16, 1946

CHILDREN'S BUREAU INDUSTRIAL DIVISION MADE A PART OF  
LABOR DEPARTMENT'S DIVISION OF LABOR STANDARDS

Secretary of Labor L. B. Schwellenbach announced today that the Industrial Division of the Children's Bureau, which under the President's Reorganization Plan No. 2 remains in the Department of Labor while the rest of the Bureau moves to the Federal Security Agency, is being transferred as a unit to the Department's Division of Labor Standards.

In its new setting, the unit will be known as the Child Labor and Youth Employment Branch of the Division of Labor Standards. It will be directed by Beatrice McConnell who will be made an Assistant Director of this Division. Miss McConnell has been with the Children's Bureau since 1935, and has been the person responsible, under the Chief of the Children's Bureau, for the administration of the child-labor provisions of the Fair Labor Standards Act since its passage in 1938.

"I am transferring the Children's Bureau Industrial Division as a unit because I want the Department of Labor to continue its leadership in promoting the welfare of young workers, and this Division has behind it a notable record of achievement in this respect," Secretary Schwellenbach said. "In accordance with the terms of the Reorganization Plan, which transfers the Bureau's child-labor functions to my office, I am delegating these responsibilities to be performed by the new Child-Labor and Youth-Employment Branch in close relationship with the Department's Wage and Hour Division which administers the rest of the act."

In addition to these responsibilities, the new Branch will be expected to promote better working conditions for minors, develop and promote standards for their employment protection, and measures for advancing their opportunities for suitable work. It will advise with other bureaus in the Department and with State and other public and private agencies and with individuals on these and other matters affecting young workers. In these activities, the Branch will cooperate with the Children's Bureau work in the broad field of child health and welfare.

Miss McConnell, who is a graduate of the University of Wisconsin, has had wide and varied experience in the field of employment for women and children. For 10 years she served in the Bureau of Women and Children of the Pennsylvania Department of Labor and Industry, first as Assistant Director and later as Director. She served as a member of the Committee on Housing of Migratory Workers of President Roosevelt's Conference on Home Building and Home Ownership, and represented the State of Pennsylvania on the Interstate Migratory Child Labor Committee. She played an active part in the National Committee on Hazardous Occupations for Minors in 1932, and served as a member of the 1940 White House Conference on Children in a Democracy. Miss McConnell was appointed Technical Advisor of the U. S. Government Delegation to the International Labor Organization, held in Havana, Cuba, in 1939, and in Mexico City in April, 1946.

## Comment

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On June 22 ten of the eleven members of the Editorial Board of the JOURNAL spent the day in St. Louis discussing JOURNAL policies and plans for the future. Only three of the present eleven members of the Board were members of the original Board appointed by the Academy in 1932.

From both the editorial and publishing standpoints the war brought many problems to the JOURNAL which are just now beginning to straighten out.

Certain specific changes were decided upon which are of importance to authors submitting manuscripts for publication and to JOURNAL readers.

1. In the future the metric system for weights and for doses of drugs will be used in the text corresponding to the usage in the *U. S. Pharmacopoeia*.
2. References to literature should include the title of the article as well as the numerical reference to the volume, page, and year of the journal.
3. Titles to articles should have the term used in *The Quarterly Cumulative Index of Medicine*. Thus for example, use Poliomyelitis, not Infantile Paralysis; Whooping Cough, rather than Pertussis.

The JOURNAL will continue its past policy of broad coverage of the entire field of pediatrics. The return of pediatricians from service and the deceleration of the teaching in our medical schools and clinics, should relieve the shortage of and strain on the personnel in our hospitals and clinics and lead to pediatric research going ahead again as it did during the late thirties. The JOURNAL publishes approximately 150 articles a year. In 1940, 270 manuscripts were submitted for publication allowing a wide choice in selection by the Editorial Board. By 1944 the number submitted fell to 136. A marked increase has taken place in the first half of the present year. The situation during the war was not in any way unique for the JOURNAL but affected all medical publications.

# The Journal of Pediatrics

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## Original Communications

### ORAL MANIFESTATIONS OF CONGENITAL HEART DISEASE

#### A PRELIMINARY REPORT

ABRAHAM KANER, B.S., D.M.D., PAUL K. LOSCH, D.D.S., AND  
HYMAN GREEN, M.D.  
BOSTON, MASS.

IN A CLINIC devoted to congenital heart disease it was noted by one of us (H. G.) that children with marked cyanosis complained occasionally of toothache. To explain this symptom the dental department was consulted. This study was then undertaken to demonstrate the marked changes which occurred in the buccal mucous membrane, gingivae, and tongue as a result of circulatory congestion.

The diagnoses of the congenital heart malformations were made after careful consideration of the clinical, roentgenographic, and electrocardiographic findings.<sup>1</sup>

One hundred and thirteen children presenting different types of congenital heart disease were examined at The Children's Hospital, Boston. These patients varied in age from 10 months to 12 years. Among the children examined, eighteen had the tetralogy of Fallot; seven, coarctation of the aorta; three, dextrocardia; four, transposition of the great vessels; sixteen, patent ductus arteriosus; fifty-two, septal defects; ten, persistent ostium primum; and three, tetralogy of Eisenmenger.

The lips, cheeks, oral mucous membranes, tongue, gingivae, teeth, pharyngeal fauces, and occlusion of these children were examined. Bite wing and periapical x-rays were taken on all individuals except where not possible due to extreme youth.

We have grouped our findings under the different conditions presented:

1. *Tetralogy of Fallot*.—The most striking oral observations were seen in this group of children. The tetralogy of Fallot is characterized by (a) pulmonary stenosis, (b) enlargement of the right ventricle, (c) defect in the interventricular septum, and (d) dextroposition of the aorta.<sup>2</sup>

1. *Lips*: The mucous membranes of the lips were purplish-blue in color. The cyanosis was very marked in all patients.

From the Harvard Medical School, Harvard School of Dental Medicine, the Dental and Cardiac Clinics of The Children's Hospital.

2. *Buccal mucous membranes:* The mucous membranes of the cheeks were dark bluish-red. The membranes had a pronounced wrinkling. It is our opinion that this wrinkling indicates a transient edema.
3. *Gingivae:* In all cases, a severe marginal gingivitis was present. The gingivae were dark bluish-red and very markedly inflamed. Bleeding was produced on very slight pressure (e.g. mechanical or digital). This gingivitis was generalized, but the gingivae in the anterior portion of the maxilla (from cuspid to cuspid) were more seriously involved.
4. *Tongue:* The dorsum of the tongue in these patients presented a very bright bluish-red appearance. The tongues were deeply fissured and edematous. The middle and posterior thirds were heavily coated with a smooth, brownish-white, closely adherent material. The fungiform and filiform papillae were markedly raised, very prominent, and extremely reddened. In three cases, atrophy of the filiform and fungiform papillae was noted. The blood vessels on the inferior surface of the tongue were very prominent. This tongue has been appropriately called a "chow" tongue. (Figs. 1 and 2.)
5. *Floor of mouth and pharyngeal fauces:* Marked cyanosis of both of these structures was noted.
6. *Occlusion:* The occlusion in these patients was found to be normal. However, several cases were observed which presented a marked anterior overbite. Our period of observation has not been long enough to determine the significance of this condition.
7. *Teeth:* The teeth in these children were found to be normal in size and shape. However, in most cases there was a delay in the eruption time of both the deciduous and permanent teeth. One case was seen in which a spontaneous abortion of the crowns of the maxillary incisor teeth occurred at 18 months of age. Continued studies are being made on the chronology of tooth eruption.

In all cases observed, the incidence of carious lesions of the teeth was markedly elevated.

Several teeth were extracted under topical anesthesia, and histologic sections revealed that there was a dilatation and engorgement of the capillaries in the dental pulp. Rupture of several capillaries was noted with an escape of red and white blood corpuscles into the connective tissue stroma of the pulp. The predentin layer was abnormal and the dentine was poorly calcified. The odontoblastic layer was irregular and several odontoblastic cells were pyknotic. The pulp was edematous. (Figs. 3 and 4.)

8. *X-rays:* Bite wing and periapical x-rays revealed that the alveolar bone and basal bone displayed no appreciable changes.

II. *Tetralogy of Eisenmenger.*—In the tetralogy of Eisenmenger there is less cyanosis and clubbing than in the tetralogy of Fallot. In the Eisenmenger type there is hoarseness, while this symptom is absent in the Fallot type. There is also a pulmonary insufficiency with a diastolic murmur in this condition. The

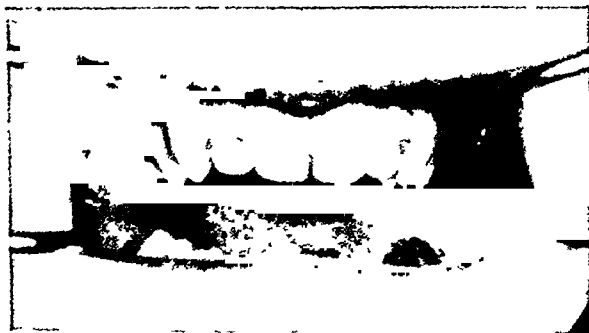


Fig. 1.

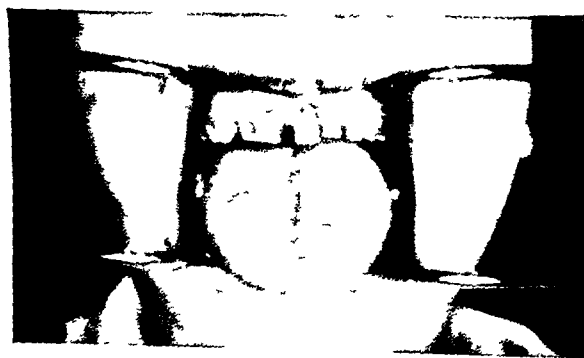
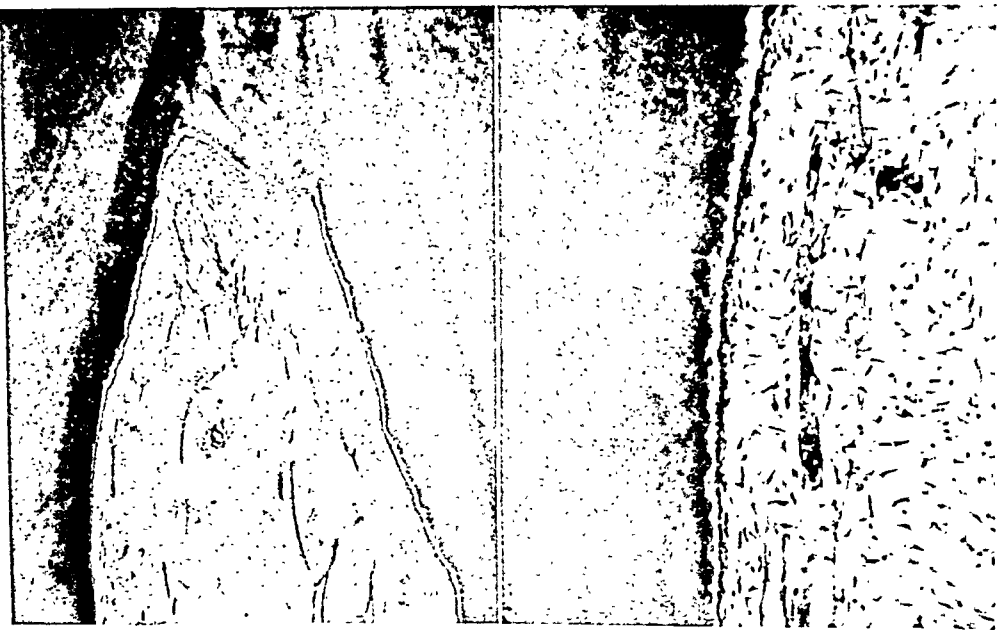


Fig. 2.

Figs. 1 and 2.—Illustrating the marked cyanosis of the lips, buccal mucous membrane, and tongue. In addition, note the prominence and extreme redness of the filiform and fungiform papillae. Fig. 1 is an 8-year-old child, Fig. 2 is a 10-year-old child.







Figs. 3 and 4.—Showing low- and high-power views of extracted teeth, displaying a marked engorgement of the capillaries in the pulp. Also note the predentin and the irregular odontoblastic layer.

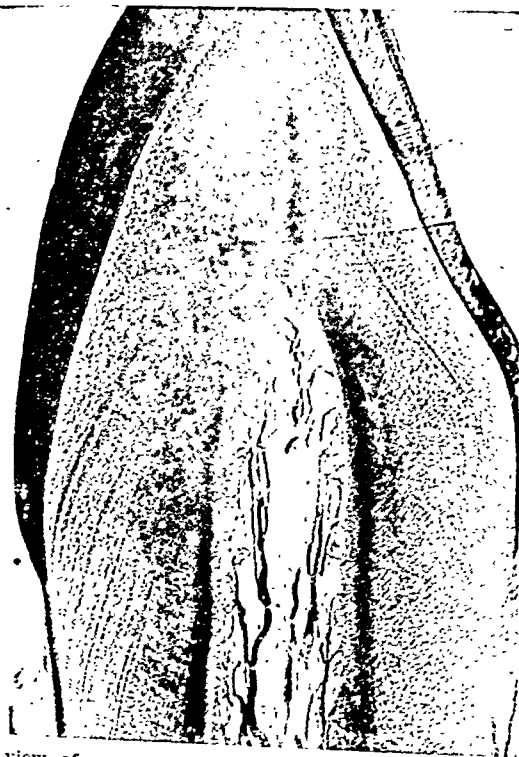


Fig. 5.—Low-power view of a post-mortem disassociated tooth displaying marked engorgement of the capillaries in the dental pulp.

x-ray picture is characteristic, since the pulmonary artery in the Eisenmenger type shows a bulge in the region of the conus, as contrasted to an absence of shadow in the tetralogy of Fallot.

The lips, cheeks, and buccal mucous membranes were markedly cyanotic, but the cyanosis was less severe than that seen in the Fallot type. There was a very severe generalized marginal gingivitis, and the appearance of the gingivae was similar to that seen in the tetralogy of Fallot. The tongue presented the same clinical appearance as that seen in the Fallot type. Periapical and bite wing x-rays appeared normal.



Figs. 6, 7, and 8.—Ages 3, 8, and 12 years, respectively, illustrating the markedly enlarged, funnel-shaped pulp canals in the maxillary central and lateral incisor teeth.

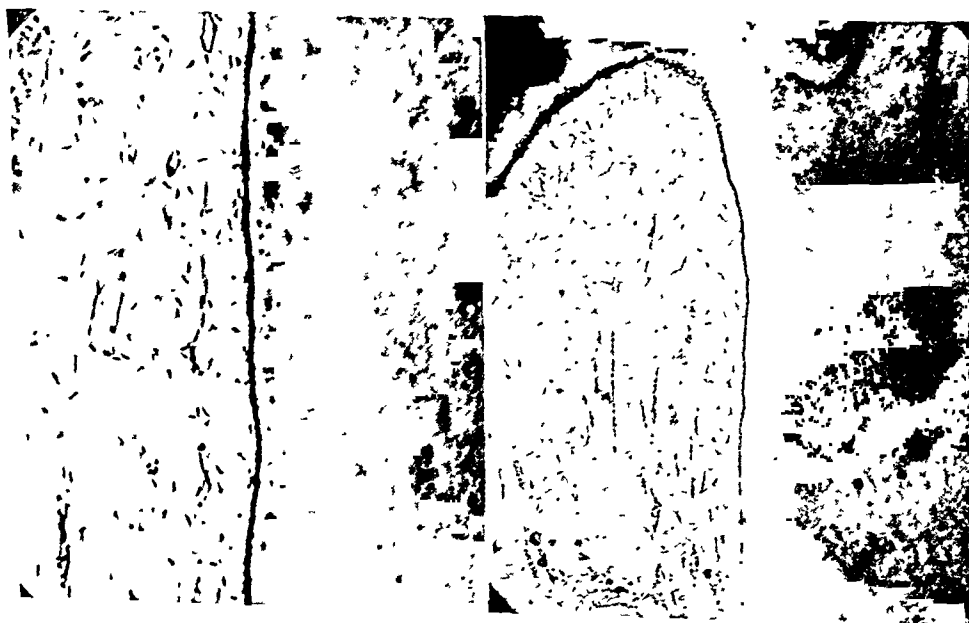
III. *Transposition of the Great Vessels*.—In these cases it is found that the aorta arises from the right ventricle and the pulmonary artery from the left.

In four cases which presented transposition of the great vessels, it was found that a less severe marginal gingivitis existed than was observed in the tetralogy of Fallot. The gingivitis was generalized. The lips, cheeks, buccal mucous membranes, floor of the mouth, pharyngeal fauces, and tongue had a similar appearance to that seen in the tetralogy but the cyanosis was less marked. X-ray examination revealed no observable defects.

Histologic examination of the teeth revealed that the pulp was edematous and the blood vessels were markedly dilated and engorged with blood cells. (Fig. 5.)

IV. *Coarctation of the Aorta*.—This condition is characterized by a narrowing of the aorta in the region where it is joined by the ductus arteriosus. Clinical examination of these individuals revealed that the gingivae of the premaxilla were markedly reddened and inflamed. There was no wrinkling and no edema of the mucous membranes. The caries index was usual for this age group and geographic area and no consistent abnormalities of occlusion were noted.

Periapical x-rays revealed the pulps of the four maxillary incisors (deciduous and permanent) to be markedly enlarged. They were funnel-shaped, occupying a great portion of the crown and root of each tooth. The selection of these teeth alone for this abnormality is not yet understood. The pulps of the molar teeth appeared to be normal in size and shape. (Figs. 6, 7, and 8.) It is our opinion that this enlargement of the root canals may be due to the marked arterial hypertension which characterizes this condition. This was the



FIGS. 9 and 10.—Microscopic views of a tooth recovered from a patient with coarctation of aorta.

only type of congenital heart disease examined by the authors in which such an observation was made.

Histologic examination of the teeth revealed that the capillaries in the pulp were markedly dilated and prominent. The dentine was poorly calcified. The predentin layer appeared normal in width. The odontoblastic layer was regular and the cells were normal in shape and size. Several vacuoles were present in the pulp which were sparsely lined with a single layer of flattened cells and were not judged to be lymphatic channels. (Figs. 9 and 10.)

V. *Dextrocardia*.—In dextrocardia, the heart is located in the right chest, and in three cases no demonstrable deviation from the normal was observed in the oral cavity or surrounding structures.

VI. *Patent Ductus Arteriosus*.—Sixteen children were seen in which the ductus arteriosus failed to become obliterated. We observed no oral symptoms clinically and no apparent changes were noted on x-ray examination.

VII. *Septal Defects*.—Fifty-two children presenting interauricular and interventricular septal defects were seen. We observed no evident abnormalities on clinical and x-ray examination.

VIII. *Persistent Ostium Primum*.—Clinical examination of these individuals revealed that the gingivae showed a slightly glazed appearance of the interdental papillae. The papillae were slightly reddened. This redness was more marked in the maxillary incisor region. The papillae of the tongue were prominent and slightly reddened. The tongue in these individuals had a greyish-white coating. No other clinical observations on the mouth and teeth were significant. The authors observed no abnormalities on x-ray examination.

SUMMARY

1. A description and discussion is given of the observations made on the teeth and surrounding structures as seen in the following conditions: tetralogy of Fallot, coarctation of the aorta, dextrocardia, transposition of the great vessels, patent ductus arteriosus, septal defects, persistent ostium primum, and tetralogy of Eisenmenger.

2. The most striking changes are observed in the papillae of the tongue, the mucous membranes, and gingivae in the tetralogy of Fallot. Similar but less marked changes in these structures are seen in the tetralogy of Eisenmenger, and in transposition of the great vessels. In coarctation of the aorta the pulp canals in the maxillary incisors are found to be markedly enlarged and funnel-shaped.

3. No observable oral manifestations were noted in dextrocardia, patent ductus arteriosus, and septal defects.

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REFERENCES

1. Green, H.: New York State J. Med. 45: 877, 1945.  
2. Boyd, W.: A Text-Book of Pathology, ed. 3, Philadelphia, 1938, Lea & Febiger, pp. 422-425.

# THE USE OF A SULFADIAZINE-SULFATHIAZOLE MIXTURE IN THE TREATMENT OF CHILDREN

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## INTRODUCTION

DESPITE the advent of penicillin, the sulfonamides will undoubtedly continue to play an important role in the therapy of human infections. The reasons become obvious if one considers briefly the comparative merits of penicillin and the sulfonamide compounds.<sup>1-6</sup> With the exception of staphylococcal septicemia and the treatment of infections due to nonhemolytic streptococci and streptococci of the viridans type, penicillin has not proved superior or only slightly superior to the sulfonamides commonly employed at present in bacterial infections. The sulfonamides, furthermore, are effective against the primary and secondary invaders of bacillary dysentery, *Escherichia coli*, and to some extent also against *Bacillus proteus*, *Bacillus pyocyaneus* and *Hemophilus influenzae*, whereas penicillin is ineffective against these organisms. In addition, penicillin fastness is being observed with increasing frequency.

In the light of these considerations, it appears highly desirable to continue all efforts which might lead to elimination or at least diminution of serious toxic reactions caused by the sulfonamides. The most dreaded of these are damage to the blood-building organs and renal complications. The first, which may lead to agranulocytosis, is fortunately rare; it can neither be anticipated nor prevented, although reduction in the total period of therapy might possibly decrease the incidence of damage to the hematopoietic system. Kidney lesions, on the other hand, are encountered frequently. They are caused predominantly by intratubular deposition of sulfonamide crystals, in other words by a mechanical factor; their incidence is, therefore, amenable to reduction with the help of adequate precautionary measures.

The precipitation of sulfonamides in the urinary tract is largely dependent upon the solubility and concentration of these compounds in the tubular urine. Hence, any measure increasing the solubility or preventing high urinary concentrations of the sulfonamides, should tend to diminish the incidence of drug precipitation in the urinary tract. Such measures generally employed at the bedside are the "forcing of fluids" which prevents high urinary concentration of the sulfonamides, and alkalization of the urine which increases their solubility.

Recently it was found by one of us that effective prevention of renal complications could be obtained by the therapeutic employment of sulfonamide mixtures instead of individual compounds. The observation had its origin in solubility studies with various mixtures of sulfonamides. These revealed that two or more of these compounds, when present simultaneously in water or

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urine, did not have any influence upon each other with regard to their individual solubilities. In other words, sulfathiazole, sulfadiazine, and sulfamerazine, for example, could be dissolved *simultaneously* in the same sample of water or urine to the point of full saturation of each compound when present alone. The concentration of the three drugs in a saturated solution represented, therefore, the sum total of their individual solubilities. It was reasoned that the danger of intrarenal precipitation or concrement formation from the sulfonamides comprising such a mixture "should only be as great as if each compound had been administered alone, and in the partial dosage contained in the mixture." The validity of this conception was substantiated in animal experimental studies as well as in clinical trials.<sup>7, 8</sup>

Extensive absorption-excretion studies in experimental animals, using various sulfonamide mixtures and different routes of administration, established a more complete absorption and elimination of drug combinations as compared with single compounds. The blood levels were accordingly higher than was expected from theoretical computations.

The in vitro antibacterial activity of sulfonamide mixtures was found to correspond largely to the total concentration of free sulfonamide. In some instances mixtures were even distinctly more effective than any of their components in identical concentration.<sup>7</sup>

On the basis of these experimental and preliminary clinical observations, we extended the therapeutic use of the sulfadiazine-sulfathiazole combination to a large group of infants and children.

#### THE ABSORPTION AND EXCRETION OF THE SULFONAMIDE MIXTURE IN CHILDREN

The primary purpose of these experiments was the comparative evaluation of the sulfonamide combination against the same total dosage of either of its components in the *same* individual. With the exception of a smaller dosage, the procedure employed was essentially the same as the one previously used in adults.<sup>5</sup>

*Procedure.*—Three boys were selected for this investigation:

1. V. G., 7 years, white. Diagnosis: contusion of the brain, malnutrition.
2. J. J., 8 years, Negro. Diagnosis: common cold, lymphadenitis of cervical glands.
3. E. T., 8 years, Negro. Diagnosis: peritonsillar abscess, possible rheumatic heart disease.

At the start of the study the three patients had completely recovered and had no apparent impairment of renal function as judged from urinalysis and determination of nonprotein nitrogen and urea nitrogen levels in the blood. Each child was given three consecutive single dose tests with 3 Gm. of sulfonamide in the sequence: sulfathiazole, sulfadiazine, sulfadiazine-sulfathiazole mixture. In order to obtain complete elimination of each drug from the body, an interval of two days was allowed to elapse between the administration of sulfathiazole and sulfadiazine, and an interval of four days between sulfadiazine and the mixture.

Each test was done in the following way: the fasting patient received 3 Gm. of sulfonamide (1.5 Gm. each of sulfathiazole and sulfadiazine in the third test) at 9 A.M. with one glass of milk followed by one glass of water. In order to insure equalized absorption, no further fluid and no food was permitted thereafter until noon. From then on, food and fluid intake were unrestricted; however, the latter was checked throughout the duration of the experiment. The concentration of free and conjugated sulfonamide was determined in blood and urine according to the method of Bratton and Marshall using a Klett-Summerson Photo Colorimeter. (Obviously no differentiation could be made between sulfathiazole and sulfadiazine in the mixture. However, both drugs have almost the same molecular weights, and identical concentrations of either give practically identical readings. No adjustments were, therefore, necessary in expressing mixture concentrations.) Blood samples were taken from the fingertip one hour, four hours, eight hours, twenty-four hours, and forty-eight hours after drug administration. Urine specimens were obtained as far as possible at the same intervals and their amount and specific gravity were recorded. The total urine output of every twenty-four-hour period for the entire ten days which the three tests required was collected for drug determination. No untoward symptoms were encountered in any of the tests.

*Results.*—The results of all experiments were recorded in the form of graphs, summarizing the three tests performed on each patient. The graph of Case E. T. is presented as representative of all three. As anticipated, the sulfadiazine blood level rose after four hours to about twice the height of the sulfathiazole level and this relationship continued throughout the first twenty-four-hour period. The sulfonamide mixture reached a significantly higher peak concentration than sulfadiazine alone within four hours after administration. However, because of a faster elimination, the mixture levels were not as long sustained as the sulfadiazine levels. In comparison with previous studies in adults, the mixture displayed the tendency to reach relatively higher blood levels in children (Fig. 1).

Sulfonamide concentrations in the urine from the sulfadiazine-sulfathiazole mixture were lower than those from sulfadiazine in all cases, and the urine volume higher after four to eight hours than with either compound administered separately. The acetylation in the blood ranged between 5 and 10 per cent at all intervals tested. Only after four hours the mixture gave somewhat higher values. In the urine, the degree of conjugation ranged around 10 per cent after four hours, 15 per cent after eight hours and 30 per cent after twenty-four hours. It is, therefore, assumed that in the clinical application of the mixture, the degree of conjugation would not be significantly different from the one observed with the two sulfonamides when employed separately.

The results of the absorption-excretion study confirmed the viewpoint and the experience gained in adults, that using the routine dosage and the generally accepted four-hour interval, levels as high or higher than from sulfa-



diazine alone could probably be maintained in the blood with the sulfonamide mixture. The low urine concentrations in the presence of high blood levels suggested a possible added protection for the kidney.

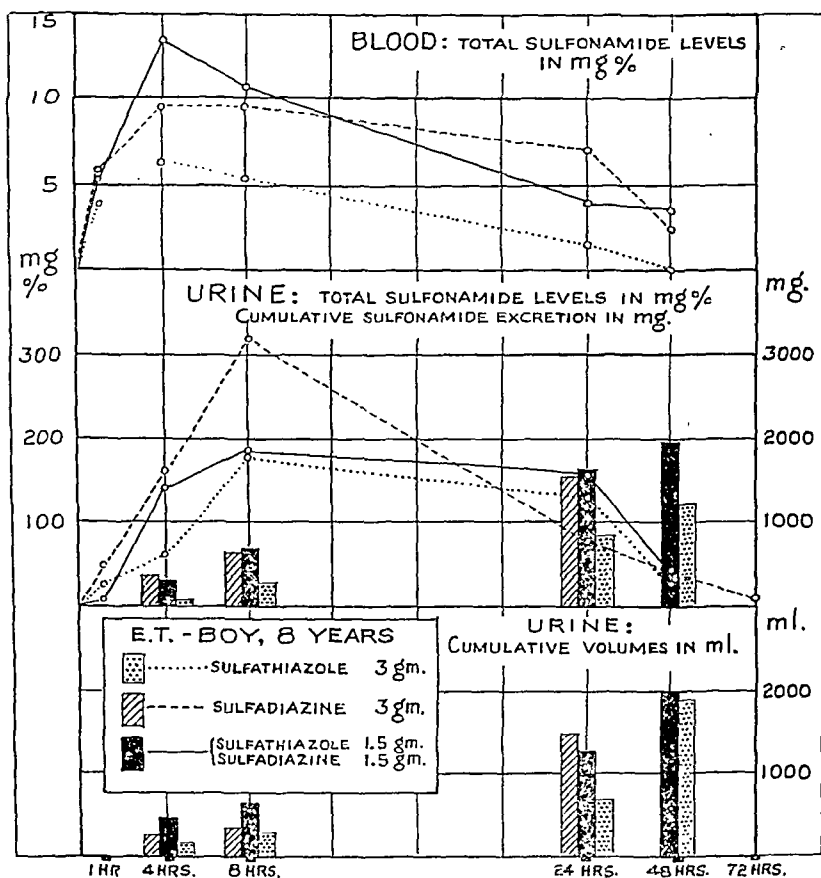


Fig. 1.—Absorption and excretion of a single oral dose of sulfadiazine, sulfathiazole, and a sulfadiazine-sulfathiazole mixture in the same individual. (The forty-eight-hour urine sample of the sulfadiazine test was lost.)

#### THE THERAPEUTIC APPLICATION OF THE SULFONAMIDE MIXTURE

Treatment with a mixture containing equal parts of sulfadiazine and sulfathiazole was carried out in more than 200 unselected children and infants with acute bacterial infections. The first 47 cases were studied under carefully controlled and standardized conditions. Special consideration was given to daily follow-up studies of the sulfonamide concentration in blood and urine, to the frequency in the occurrence of sulfonamide crystals in the urine and its relationship to the urinary pH and drug concentration, and to any signs or symptoms of renal complications. Patients treated after completion of this study on the first 47 cases were also carefully observed, but determination of the sulfonamide concentration in the blood was done only every third day and in the urine only occasionally.

From the experience gained in animal experimental studies and from the treatment of adults, it appeared safe to omit adjuvant alkali therapy. This was done in order to evaluate the protection afforded by employing sulfonamide mixtures under the increased risk of an acid urine reaction.

*Procedure.*—Before institution of therapy, information on the state of the kidney was gathered from urinalysis, and determination of the creatinine and nonprotein nitrogen level in the blood. A complete blood count was done and, whenever possible, culture material for bacteriologic diagnosis was obtained.

The sulfadiazine-sulfathiazole mixture was given orally. The first day's total dosage employed in this series was 1.5 grains of the mixture per pound (about 0.2 Gm. per kilogram) of body weight. One-third of the first day's dose was given at the onset of therapy and the remainder was divided into five equal amounts given at four-hour intervals. This maintenance dose was continued on the following day and thereafter at four-hour intervals until defervescence and other clinical signs indicated significant improvement, whereupon the interval of administration was prolonged to six hours.

The entire fluid intake and output were checked carefully. The intake was kept at  $2\frac{1}{2}$  to 3 ounces of fluid per pound per day in infants. Older children received 1,200 to 2,000 c.c. of fluid daily. In most cases it was attempted to give fluids by mouth; when this was difficult, parenteral hypodermoclyses of infusions of  $2\frac{1}{2}$  per cent glucose and physiologic saline were used. No alkalizing agents were employed at any time.

The collection of the total urine output was not attempted in infants because of obvious mechanical difficulty; however, an early morning specimen was obtained daily for determination of pH and drug concentration and for examination of the sediment for sulfonamide crystals. In larger children samples of the entire twenty-four-hour output were examined daily for specific gravity, pH (Cambridge Electron-Ray pH Meter), albumin, microscopic findings in the sediment, and drug concentration. The first morning specimen was collected separately for determination of the pH and examination of the sediment for urinary crystals. Since this specimen is usually the most concentrated and most acid, it was the most likely to contain urinary crystals. The total amount of sulfonamide excreted with the urine was estimated for every twenty-four-hour period throughout the time of drug administration.

Blood for determination of the free and total sulfonamide level was collected every morning at 9 A.M. Complete blood counts were performed every third day.

*Results.*—The first 43 cases treated with the sulfadiazine-sulfathiazole mixture are briefly summarized in tabular form (Table I), in order to indicate especially the relationship between duration of treatment, total amount of sulfonamide used, and therapeutic results observed.

Two of the cases listed in the table were chosen for graphic demonstration because of their representative illustration of absorption and excretion of the sulfonamide mixture (Fig. 2).

The most significant observations made in the 200 children under treatment with the sulfonamide mixture, can be derived from Table I and Fig. 2. Briefly summarized the findings were as follows: The therapeutic effectiveness of the sulfadiazine-sulfathiazole mixture was highly satisfactory and the period of treatment was rather short in most instances. The total amounts of sulfonamide used were consequently small. Therapeutically effective blood levels were maintained with ease and discontinuation of therapy resulted in rapid elimination of the sulfonamide mixture from the body. Conjugation figures were low, ranging as a rule between 3 and 15 per cent in the blood and 10 and 30 per cent in the urine. Crystalluria was infrequent and never "massive." Its occurrence was limited to excessive drug concentrations in the presence of an acid urine reaction. Allergic signs such as drug fever or rash were observed in only two instances. Nausea and vomiting were rare. No other toxic reactions were encountered.

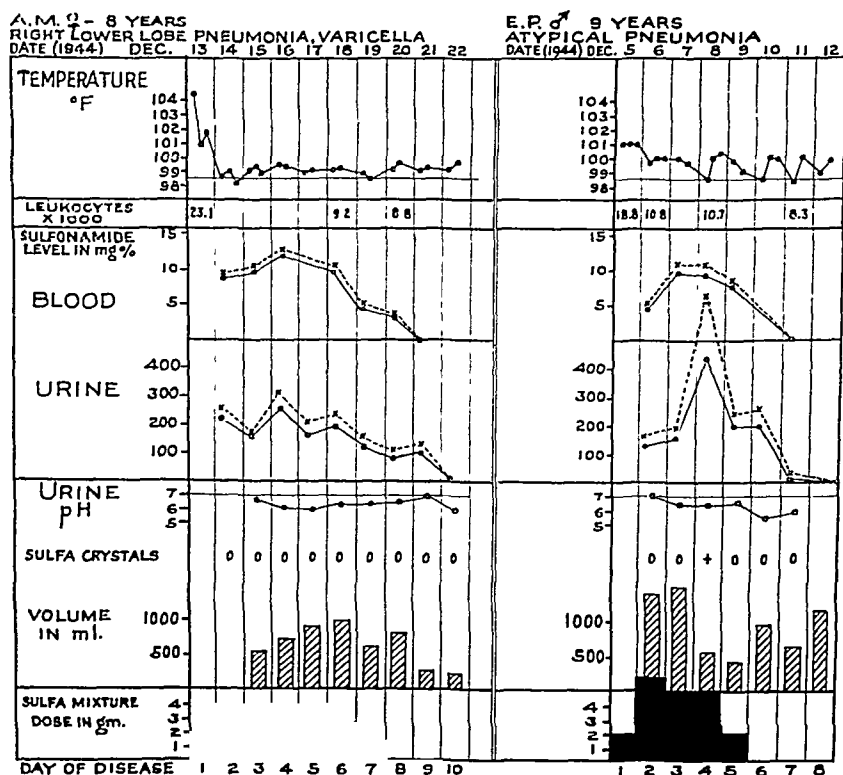


Fig. 2.—The broken lines indicate total sulfonamide concentrations. The daily temperatures were recorded at 8 A.M., 4 P.M., and 8 P.M.

#### COMMENT

When employed individually, sulfadiazine and sulfathiazole are generally recognized as the most effective sulfonamides with regard to scope and intensity of antibacterial action, and as the least troublesome with regard to sub-

jective discomfort to the patient. They are also about equally dangerous to the kidney and very similar in all other aspects of clinical toxicology, except for the higher incidence of rash and drug fever induced by sulfathiazole.<sup>9, 10</sup> These observations apply to children<sup>11</sup> as well as to adults, although renal complications occur less frequently in young individuals.<sup>12</sup>

The administration of the sulfadiazine-sulfathiazole mixture in the present study confirmed the expectation of a low clinical toxicity and remarkable therapeutic effectiveness of this drug combination. It is noteworthy, in particular, that no instance of any renal complication was encountered, despite the intentional omission of adjuvant alkali therapy. This observation is in good agreement with the fact that sulfonamide crystals in the urine were found only infrequently. The crystalluria was, in addition, not of the "massive" type observed so commonly during therapy with sulfadiazine and especially sulfathiazole.<sup>13</sup> It was emphasized in previous publications<sup>8, 14</sup> that it is primarily the mechanical factor of intratubular deposition of poorly soluble crystals which accounts for most renal complications from sulfonamides, rather than any primary chemical nephrotoxic action. The significant reduction in the tendency to oversaturation and consequently to intrarenal precipitation by the use of sulfonamide mixtures, would, therefore, sufficiently explain the absence of renal complications. However, it should be kept in mind that the protection afforded to the kidney by the employment of sulfonamide mixtures is obviously limited and should not lead to the neglect of generally accepted preventive measures such as adequate fluid intake and alkalization of the urine.<sup>3, 15</sup>

It was noted also that the sulfadiazine-sulfathiazole combination, when administered orally, resulted in blood levels as high or significantly higher than from equal amounts of sulfadiazine. According to mathematical computations (algebraic sum of sulfadiazine and sulfathiazole levels, divided by two, Fig. 1), the blood level from the mixture should be far below the sulfadiazine level. Since the urinary excretion of the mixture was usually equal to or more complete than the elimination of either sulfadiazine or sulfathiazole in identical amounts, it seems reasonable to assume that the combination was more quickly and more completely absorbed from the gastrointestinal tract than either of its components. This observation can be explained by the relatively more complete utilization of smaller amounts of drug and was borne out in standardized absorption-excretion studies with laboratory animals.<sup>16</sup> In its ease of maintaining highly effective blood levels the mixture retained the advantage of sulfadiazine, whereas its faculty of more ready elimination from the body was apparently due to the presence of sulfathiazole. A further advantage was seen in the low percentage of conjugation.

The rapid therapeutic response to the sulfadiazine-sulfathiazole mixture was its most remarkable feature. It pointed toward an actual higher antibacterial efficacy of the combination. This viewpoint is in good agreement with the actual potentiation of therapeutic activity observed *in vitro* with mixtures of two or more sulfonamides.<sup>7</sup> It was this high effectiveness of the mixture which induced us to attempt discontinuation of therapy more abruptly

TABLE I

CASE	AGE (YR.)	SEX	RACE	DIAGNOSIS	DAYS OF TREAT- MENT	DEFER- VES- CENCE AFTER DAYS	TOTAL SULFA DOSE (GM.)	REMARKS
1. J. G.	4	M	W	Bronchopneumonia, im- petigo	6	1	16.0	Recovery
2. J. V.	5	M	W	Bronchiolitis, pleural effusion	5	3	19.0	Recovery
3. J. S.	8½	M	W	Follicular tonsillitis	3	1	11.6	Recovery
4. A. I.	1½	M	W	Bacillary dysentery ( <i>Shigella sonnei</i> )	6	1	16.5	Recovery
5. R. Q.	3	M	W	Follicular tonsillitis, tracheobronchitis, con- genital heart disease	4	2	14.5	Recovery
6. F. R.	2	M	W	Bronchiolitis	5	1	11.2	Recovery
7. M. B.	5	F	N	Tracheobronchitis	5	3	19.1	Recovery
8. J. G.	6	F	W	Lobar pneumonia (R.M.L.)	10	2	32.6	Recovery
9. A. A.	¾	F	W	Bronchiolitis, nutritional anemia	2	1	2.9	Recovery
10. E. P.	9	M	W	Atypical pneumonia	5	-	18.9	Tempera- ture varied between 98.6 and 100.4° F. for 16 days
11. A. M.	8	F	W	Lobar pneumonia (R.L.L.), varicella	6	1	23.3	Recovery
12. R. V.	¾	M	W	Bronchiolitis, otitis media	3	1	9.0	Recovery
13. J. C.	1½	M	W	Bronchiolitis, otitis media	5	1	13.2	Recovery
14. W. B.	1½	M	W	Pyelonephritis, <i>B. pyo- cyanous</i>	9	5	21.0	Recovery
15. J. E.	½	M	W	Pneumonitis (R.V.L.), pleurisy	3	1	3.6	Recovery
16. M. R.	3½	F	W	Follicular tonsillitis, cer- vical adenitis	4	2	13.2	Recovery
17. C. P.	2½	F	W	Purulent otitis media	5	3	13.7	Recovery
18. M. B.	10	F	W	Follicular tonsillitis, cer- vical adenitis	2	1	9.0	Recovery
19. R. G.	2	M	W	Tonsillitis, tracheobron- chitis	6	4	15.6	Recovery
20. M. W.	6	M	W	Atypical pneumonia, pharyngitis, <i>B. hemo- lytic streptococcus</i>	5	3	21.2	Recovery
21. G. D.	1½	M	W	Tonsillitis, otitis media	7	2	11.6	Recovery
22. M. R.	4	F	W	Primary childhood tuber- culosis	2	3	13.6	Sulfa dis- continued when it was discov- ered child had tuber- culosis

than is recommended as the routine procedure with single sulfonamides. Although this was done consistently, reinstitution of therapy was not found necessary in any of the cases treated.

With regard to allergic reactions, one would expect an increase in their incidence from the simultaneous employment of two sulfonamides. However, this assumption was not borne out by our experience. The two cases exhibiting allergic reactions represent an incidence of only 1 per cent. This is significantly lower than the values reported in the literature for sensitization

TABLE I—CONT'D

CASE	AGE (YR.)	SEX	RACE	DIAGNOSIS	DAYS OF TREAT- MENT	DEFER- VES- CENCE AFTER DAYS	TOTAL SULFA DOSE (GM.)	REMARKS
23. N. V.	6	F	W	Follicular tonsillitis	3	1	9.3	Recovery
24. J. T.	3	M	W	Otitis media	6	4	16.5	Recovery
25. C. S.	$\frac{2}{3}$	F	W	Bronchiolitis	5	1	8.8	Recovery
26. S. L.	$\frac{1}{2}$	M	W	Bronchiolitis	3	2	6.0	Recovery
27. D. R.	$\frac{1}{2}$	M	W	Otitis media	3	1	5.8	Recovery
28. E. S.	2	M	W	Otitis media, tracheobron- chitis, meningism	7	3	16.5	Recovery, developed sulfa rash
29. E. R.	11	M	W	Follicular tonsillitis	3	1	20.5	Recovery
30. S. R.	7	F	W	Tracheobronchitis	3	1	8.0	Recovery
31. A. R.	1	F	W	Multiple rat bites, pul- monary tuberculosis	8	—	13.4	Sulfa dis- continued when pul- monary tuberculo- sis discov- ered
32. J. G.	6	M	N	Lobar pneumonia (R.U.L.)	8	1	13.7	Recovery
33. A. S.	$\frac{3}{4}$	M	W	Pneumonitis, nutritional anemia	2	—	3.8	After 48 hours of sulfa the child showed little re- sponse clinically
34. R. R.	3	M	W	Tonsillitis, cervical adenitis	5	2	17.5	Recovery
35. C. G.	1 $\frac{1}{2}$	F	N	Vincent's gingivostoma- titis	4	1	6.0	Recovery
36. J. T.	1 $\frac{1}{2}$	M	N	Bronchiolitis	2	1	6.3	Recovery
37. P. M.	1	F	W	Tonsillitis	4	2	8.0	Recovery
38. C. S.	1 $\frac{1}{2}$	M	W	Otitis media	2	1	4.9	Recovery
39. J. A.	$\frac{3}{4}$	M	N	Bronchiolitis	3	1	2.1	Recovery
40. A. A.	1	F	W	Bronchiolitis	5	2	12.1	Recovery
41. A. M.	8	M	N	Pyelitis, micrococcus tetragenous with meningism	6	2	24.6	Recovery
42. P. B.	1	M	W	Bronchiolitis, nutritional anemia	5	1	9.0	Recovery
43. E. M.	1	F	W	Tonsillitis, tracheobron- chitis	3	1	4.6	Developed morbilli- form erup- tion 24 hours after ad- mission. Disap- peared in 24 hours

from either sulfadiazine or sulfathiazole.<sup>8, 11, 12</sup> The low incidence of drug allergy was explained previously<sup>8</sup> by the fact that the rapid therapeutic response to the sulfadiazine-sulfathiazole mixture obviated, as a rule, the prolongation of medication beyond the time when sensitization reactions are bound to occur most frequently.

The employment of sulfonamide combinations eliminates, in addition, the necessity of determining the "drug of choice" in each particular instance, since with the exception of meningeal involvement, a sulfadiazine-sulfathiazole combination should prove highly effective in all cases requiring sulfonamide therapy. Experimental work and preliminary clinical trials suggest that for the treatment of meningitis, sulfadiazine should be combined with a sulfonamide, such as sulfamerazine, which diffuses better than sulfathiazole through the hematocephalic barrier.

Lastly, the use of sulfonamide mixtures is simple and does not entail any additional work for the nursing personnel. This is especially true if the two sulfonamides are combined into one tablet or powder.

Our results suggest that the simultaneous employment of two or more sulfonamides should replace the use of single compounds, since mixtures combine a high therapeutic efficacy with a significantly lowered toxicity.

#### SUMMARY

1. A mixture containing equal parts of sulfadiazine and sulfathiazole was investigated with regard to its absorption, excretion, therapeutic efficacy, and toxicity in children and infants.

2. The sulfadiazine-sulfathiazole mixture was quickly absorbed from the gastrointestinal tract and readily eliminated by way of the kidneys. Peak levels as high or higher than from equal weight amounts of sulfadiazine were reached in the blood within four hours after drug administration.

3. The therapeutic results with the sulfonamide combination in 200 children with acute bacterial infections were uniformly satisfactory and conspicuous in many instances because of the speed of clinical improvement and cure.

4. The clinical toxicity of the sulfadiazine-sulfathiazole mixture was remarkably low. Crystalluria was infrequent, despite the intentional omission of adjuvant alkali therapy and no signs of renal irritation were encountered. The incidence of allergic reactions also appeared decreased.

5. The mechanism leading to reduction of toxicity and higher therapeutic efficacy by the employment of sulfonamide mixtures, instead of single compounds, is discussed.

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#### REFERENCES

1. Samper, B. A., and Finland, M.: Present Day Specific Treatment of Pneumonias, *M. Clin. North America* 28: 1067, 1944.
2. Infectious Diseases: Tenth Annual Review of Significant Publications, *Arch. Int. Med.* 74: 280, 1944.
3. Lowell, F. C.: The Present Status of Sulfonamide Therapy, *M. Clin. North America* 29: 1306, 1945.
4. Collin, M. F., Sellers, A. L., and Kast, E. C.: Combined Penicillin and Sulfadiazine Therapy in Pneumococcal Pneumonia, *Am. J. M. Sc.* 211: 299, 1946.
5. Editorial: Penicillin in Pneumonia, *Lancet* 249: 819, 1945.
6. Anderson, T., and Ferguson, M. S.: Comparative Effect of Sulphonamide and Penicillin in Pneumonia, *Lancet* 249: 805, 1945.
7. Lehr, D.: Inhibition of Drug Precipitation in the Urinary Tract by the Use of Sulfonamide Mixtures. I. Sulfathiazole-Sulfadiazine Mixture, *Proc. Soc. Exper. Biol. & Med.* 58: 11, 1945.

8. Lehr, D.: The Prevention of Renal Complications by the Therapeutic Employment of Sulfonamide Mixtures. I. Sulfathiazole-Sulfadiazine Combination, *J. Urol.* 55: 549, 1946.
9. Spink, W. W.: Sulfanilamide and Related Compounds in General Practice, Chicago, 1943, The Year Book Publishers, Inc., pp. 31-39.
10. Van Dyke, H. B.: The Toxic Effects of Sulfonamides, *Ann. New York Acad. Sc.* 44: 477, 1943.
11. Dowrie, J. O., and Abramson, M. H.: Comparative Toxicities of Sulfadiazine and Sulfathiazole in Children, *J. PEDIAT.* 24: 176, 1944.
12. Fink, W. H., and Smith, C. A.: Incidence of Reactions to Sulfonamide Drugs in Infants and Children, *J. PEDIAT.* 28: 40, 1946.
13. Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H.: Sulfadiazine and Sulfathiazole in the Treatment of Pneumococcal Pneumonia; A Progress Report on 200 Cases, *Am. J. M. Sc.* 201: 585, 1941.
14. Lehr, D.: Experimental and Clinical Studies With Sulfacetimide (p-amino-benzene-sulfonylacetyl-imide): Toxicity and Efficiency in Bacillary Infections of the Urinary Tract, *J. Urol.* 54: 87, 1945.
15. Gilligan, D. R., Garb, S., Wheeler, C., and Plummer, N.: Adjuvant Alkali Therapy in the Prevention of Renal Complications From Sulfadiazine, *J. A. M. A.* 122: 1160, 1943.
16. Lehr, D.: To be published.



## TO WHAT EXTENT DOES FLUORINE INGESTION LESSEN TOOTH DECAY?\*

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VARIOUS studies have been published relating to the lessened incidence of tooth decay in communities where the domestic water supplies contain notable amounts of fluorides. It has become generally accepted that an inverse relationship obtains between the fluoride content of the public water supply and the average amount of caries observable in the corresponding population. Numerous reports have been published, presenting systematic analysis of the dental conditions of children living under diverse conditions as related to the presumed level of fluoride ingestion.<sup>1-7</sup> The data as reported in the publications cited have dealt principally with the proportion of the children studied who were free from caries, and with the average number of carious teeth for each 100 children examined.

It seems important to study further the interrelationship between fluoride exposure and caries experience. In view of the strong promotional campaigns now under way to provide for fluorinization of public water supplies as a caries-preventive measure, it would be of value to know in more quantitative terms how much reduction of caries may be expected through such a measure, and the variability to be expected from one community to another. Greater insight would be gained if the values were expressed not only in terms of group averages, but also in terms of the predicted number of children who would or would not show notable amounts of caries under the designed regimen of fluoride intake. Moreover, further data are needed to indicate whether current ingestion of fluoride may be expected to lessen caries incidence in the permanent dentition, as compared with the effect which one may observe in children whose fluoride ingestion occurs throughout the time of crown formation of the permanent teeth.

Certain communities in Iowa provide favorable facilities for the study of the effect of fluorine ingestion. Numerous wells in the State contain notable amounts of fluoride; quantities in excess of a trace have been reported from wells in all but seven of the State's 99 counties. In 44 of the counties, amounts of 1 part per million or more have been reported, and in 26 counties the recorded analyses show an average of 1.5 parts per million or more.

During the summer of 1944, the authors conducted detailed dental surveys in a region of endemic fluorosis, and in three State-controlled custodial institutions for children. The population studied was limited to subjects who were 13 years old or older. The dental findings have been analyzed not only in terms of place of residence and the regional content of fluoride in the domestic water

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supplies, but also on the basis of whether or not mottling of enamel was evident. Dental data have been expressed in terms of the number of surfaces of permanent teeth which have been affected by decay. The analysis has been made in terms of the frequency distribution of caries scores among the members of the groups as well as the average values for caries incidence. Included were counts of the number of *Lactobacillus acidophilus* organisms in the saliva of individual subjects. The results of the analysis of data indicate a significant inverse relationship between the incidence and extent of caries and the presence of mottling, but the distinction between the contrasted groups is not great: The ratio is approximately as 3:4, in favor of those children with mottled enamel. The average caries score of the subjects without mottled enamel was notably high, similar to that of the average child population elsewhere. Moreover, there is no evidence from the data obtained that the posteruptive ingestion of fluoride-containing water has lessened the caries incidence in the subjects examined.

#### PRESENTATION OF DATA

This study represents part of a larger program, designed to obtain accurate and detailed records of the dental status of teen-aged Iowa children, and to relate the dental findings to definable constants or variables in the environment. In this report consideration is limited to the manner in which dental caries was associated with the presence or absence of mottled enamel, and with the opportunity for current and for past ingestion of fluoride-containing water.

The three custodial institutions studied included two large orphanages and an industrial school for boys. None of the domestic water supplies in these institutions provides more than a trace of fluoride. The fourth center of study was the high school population of Ankeny, Iowa. Ankeny is a town of about 800 inhabitants situated in Polk County, about eight miles north of Des Moines. Polk County water tends to be high in fluorine content. From the records of the State Department of Health and the State Geological Survey,<sup>5</sup> fluorine values for 64 Polk County wells are available. Practically none of the domestic wells reported were free from fluoride; the median value recorded was 2.0 parts per million. Twenty rural wells within a radius of eight miles from Ankeny gave fluorine values ranging from 0 to 6.4 parts per million. Even the wells of less than 100 feet depth gave an average value of 0.9 part per million. Prior to 1936, the public water supply of Ankeny contained from 6 to 7 parts per million of fluorine, and mottling of enamel was prevalent among children who received such water during the time of the formation of the crowns of their permanent teeth. Since 1936, those wells have not been used; new wells have provided water with 0.8 to 1 part per million of fluorine.

To give full meaning to this study, one should know the specific fluoride intake for each subject from birth to the time of his dental examination. This has not been uniformly possible. For the institutionalized children we were able to learn from the official records how long each child had been resident in the institution; nothing was learned of the earlier life of these subjects. Many of these children, however, came from regions where fluorosis is encountered; about one-third of the institution subjects had mottled enamel. Each of the

Ankeny subjects was questioned at the time of his dental examination in regard to his earlier residence and this information has been supplemented through questionnaires sent to each child's home. For some rural Ankeny children we have evidence that the water supply has been constant since birth, that mottling is demonstrable, and have data as to the fluorine content of the specific water supply. Other children are known to have used only the public water supply in Ankeny since birth. Some children whose early life was spent elsewhere than in the Ankeny region have mottled enamel, and are known to have been reared in other areas of recognizedly significant fluoride supply.

The examining team comprised a dentist and a clerk. The dentist\* had been specially trained in the technique of examination desired, and had a particular interest in the recognition of stains and of mottling. Each dental examination was detailed and exacting, and required from fifteen to twenty-five minutes for its completion and recording. The dental record provided data as to the status of each tooth space and each tooth surface, not only of the presence of decay but also of the approximate extent of each dental lesion.

The subjects whose records are used in this report were 210 boys and 98 girls. All subjects younger than 163 months (13½ years) were omitted from consideration. The average age was 15 years, 9 months. The distribution of subjects in each age group and from each zone of study is shown in Table I.

TABLE I. DEFINITION OF SUBJECT PERSONNEL

SOURCE OF SUBJECTS	NUMBER OF SUBJECTS													AVERAGE AGE OF SUBJECTS (MO.)
	BOYS					GIRLS					TOTAL			
	AGE: 14	15	16	17	18+	14	15	16	17	18+	BOYS	GIRLS	ALL	
State custodial institution 1	10	8	5	3	3	6	9	5	5	6	29	31	60	188
State custodial institution 2	6	16	20	25	21						88	0	88	198
State custodial institution 3	22	17	5	1	2	6	8	6	6	2	47	28	75	187
Subtotal	38	41	30	29	26	12	17	11	11	8	164	59	223	191,
High school students from Ankeny, Iowa	7	14	12	11	2	9	14	11	4	1	46	39	85	187
Totals	45	55	42	40	28	21	31	22	15	9	210	98	308	190

Table II shows the duration of residence of the subjects in the specific regions studied. Of the institutionalized children, the boys from the industrial school had the shortest average tenure. Furthermore, practically without exception these boys had reached their teens before commitment, and as a group represented a less favored socioeconomic group than did the children from the orphanages. Of the Ankeny high school students, 25 had spent their entire lives in or near Ankeny; in all, 59 subjects had spent not less than five years of the immediate past in that locality. Only nine children were recent arrivals. Twenty-eight children had spent their first six years of life in the Ankeny region, and a total of 40 had spent at least two of their first six years there. Two-thirds

\*Dr. Wah Leung, whose services were made available through the courtesy of Dr. Harold Hodge of the University of Rochester and the Carnegie Corporation.

TABLE II. RESIDENCE OF SUBJECTS AND COMMUNAL LEVELS OF FLUORINE IN WATER SUPPLIES

A. Children From State Custodial Institutions									
PLACE OF RESIDENCE	DURATION OF SUCH RESIDENCE (YR.)				FLUORINE CONTENT OF WATER SUPPLY (PPM.)				
					FOR SPECIFIC RESIDENCE	FOR MUNICIPAL SUPPLY	FOR WHOLE COUNTY		
	AVERAGE			NUMBER OF ANALYSES			PPM. OF F		
							AVER-	RANGE	
M	F	TOTAL	MIDDLE 50% OF GROUP				AGE		
State custodial institution 1	3.1	3.3	3.3	2-4	trace	trace	16	0.9	0-2.0
State custodial institution 2	2.4	0	2.0	2-3	trace	trace	17	0.4	0-2.0
State custodial institution 3	5.9	5.6	5.8	4-9	trace	trace	21	0.5	0-2.0
B. Ankeny High School Pupils in 1944									
	NUMBER OF SUBJECTS			FLUORINE CONTENT OF WATER SUPPLY (PPM.)					
					FOR MUNICIPAL SUPPLY	FOR WHOLE COUNTY			
						NUMBER OF ANALYSES	PPM. OF F		
	AVER-	RANGE							
M	F	TOTAL					AGE		
Duration of recent residence in Ankeny vicinity:				Since 1936	0.8-1.0	29	1.5	0-6.4	
5 years or longer									
2 years or longer									
Less than 2 years									
Number resident in Ankeny vicinity during part of their first six years of life:				Prior to 1936	6-7	35	2.0	0-7.0	
5 years or longer									
2 years or longer									
Less than 2 years									

of the Ankeny children had mottling of enamel. In two subjects the mottling was severe; in two others it was moderately severe; in the remaining subjects it was mild to moderate in degree.

Table II also summarizes the available information relating to the degree of prevalence of fluorine in the regional water supplies. From the prevalence and the levels of fluorine in the water from the Ankeny region, one is justified in the assumption that most children living in the Ankeny region have ingested significant amounts of fluorine during their respective periods of residence in that locality.

Table III relates to the dental findings of the subject personnel, in terms of their place of residence. The listing includes the incidence of mottled enamel, as well as the frequency and extent of tooth decay. Caries incidence is expressed in terms of the number of decayed, missing or filled tooth surfaces (DMF surfaces). Extracted teeth were scored as equivalent to three affected surfaces.

From Table III it will be noted that 36 per cent of the institutionalized children had mottled enamel, as compared with 62 per cent of the children from Ankeny. Caries in some degree was found in the mouth of practically

every child examined. Only four subjects were caries-free: two from the institutions and two from Ankeny. The average number of DMF surfaces among the institutionalized children was 12.5; for the Ankeny children the average was 11.4. The difference between the means for the institutional versus the Ankeny subjects is without statistical significance. The ratio between the number of affected surfaces and the number of affected teeth was not distinctive for the two groups of children: 1.45 versus 1.5. The incidence of extracted teeth was uniformly low (an average of 0.15 extracted teeth for each child) for the subjects from Ankeny and from the two orphanages. In contrast, the incidence of extractions among the boys from the industrial school was high: an average of 0.9 extracted teeth for each subject. This difference probably is explainable on the basis of socioeconomic distinctions, as previously mentioned. These subjects already were in their teens when committed, and their earlier dental needs had been met through extraction rather than through reparative dental measures. Klein and Palmer<sup>11</sup> have noted correlation between the incidence of extractions and the degree of socioeconomic handicap.

TABLE III. SUMMARY OF DENTAL FINDINGS

	AGE 14	15	16	17	18+	BOYS	GIRLS	ALL
<i>A. Children Living in State Custodial Institutions</i>								
Number of subjects	50	58	41	40	34	164	59	223
DMF surfaces: total	420	665	480	646	576	2098	689	2787
Average per child						12.8	11.6	12.5
Ratio of DMF surfaces to DMF teeth						1.5	1.35	1.45
Extracted teeth: number	11	18	15	11	44	85	14	99
Subjects with no caries	2	0	0	0	0	2	0	2
Incidence of mottled enamel:								
Number of subjects						52	28	80
Percentage of group						32%	47%	36%
<i>B. Children From Ankeny High School</i>								
Number of subjects	16	28	23	15	3	46	39	85
DMF surfaces: total	174	355	209	198	32	518	450	968
Average per child						11.2	11.5	11.4
Ratio of DMF surfaces to DMF teeth						1.5	1.5	1.5
Extracted teeth: number	3	1	0	9	0	3	10	13
Subjects with no caries	0	0	0	2	0	2	0	2
Incidence of mottled enamel:								
Number of subjects						28	25	53
Percentage of group						61%	64%	62%

TABLE IV. COMPARISON OF DENTAL FINDINGS IN TERMS OF THE PRESENCE OR ABSENCE OF MOTTLED ENAMEL IN EACH SUBJECT'S MOUTH

GROUP OF SUBJECTS:	MOTTLING PRESENT			MOTTLING ABSENT		
	ANKENY SCHOOL CHILDREN	INSTITUTIONALIZED CHILDREN	TOTAL WITH MOTTLING	ANKENY SCHOOL CHILDREN	INSTITUTIONALIZED CHILDREN	TOTAL WITH NO MOTTLING
Number in group	50	77	127	35	146	181
DMF surfaces:						
Median value	9	10	10	15	12	15
Middle one-half of range	4-12	5-16	5-14	7-23	7-19	8-18
Mean	9.0	11.1	10.2	14.9	14.0	14.2
S. D.	5.8	7.8	6.9	9.6	9.25	9.6
S. E. mean	0.905	0.910	0.61	1.29	0.88	0.71
Average age, months:						
Boys			181			175
Girls			183			177

Table IV was prepared by rearranging the data used in Table III, to contrast the caries experience of children with and without mottling of the enamel, and to correlate caries scores in these subgroups with their place of residence. No sex distinction is made in Table IV, inasmuch as no significant sex difference was noted in caries scores. Note that the average DMF score for children with mottled enamel was 10.2 affected surfaces, as compared with 14.2 for children with no apparent mottling. The difference between these means is highly significant. Obviously mottling in these children is associated with a distinct lessening of average caries incidence. Moreover, the same trend was evident in each of the residential groups. It is of interest that the DMF score for the children with no apparent mottling is identical with the value reported for Hagerstown children of the same age by Klein, Palmer, and Knutson.<sup>10</sup>

One might object that the DMF score may not portray the actual extent of caries, because it does not take into consideration the extent of decay in the individual affected surfaces. To determine whether fluorosis led to lessened extent as well as lessened incidence of caries, we have devised a weighted DMF score for each child. This was done by multiplying the number of affected tooth surfaces by an arbitrary coefficient, based on the amount of tooth surface involved by caries. For lesions involving less than  $\frac{1}{4}$  of the surface, the coefficient was 1; if less than  $\frac{1}{2}$ , the coefficient was 2; if less than  $\frac{3}{4}$ , the coefficient was 3; if more than  $\frac{3}{4}$  of the surface had been attacked, the coefficient was 4. Extracted teeth were given a weighted value of 12. Using this method of appraisal, then determining the ratio between the respective weighted and unweighted DMF values, no significant difference could be demonstrated between the extent of carious lesions in those with and without mottling of enamel. The average ratios between the weighted and the unweighted scores in the various residential areas for those with and without mottling ranged from 1.84 to 2.54. For the institutions collectively, such ratios for those with and without mottling were 2.3 and 2.3, respectively; for the Ankeny group the corresponding ratios were 2.24 and 2.42, with the unweighted scores considered as unity.

The total average reduction of caries incidence and extent observed in those with mottling, therefore, is expressed adequately by the unweighted values of DMF scores for the contrasted groups: those with mottling had 72 per cent as much caries as those with no mottling. Without question this is a desirable reduction, but it should be noted that the incidence of caries was considerable, even among those with mottling. One-half of the group with mottling had 10 or more DMF surfaces, and one-fourth of that group had more than 14 affected surfaces. Moreover, among the Ankeny subjects, those without mottling had a significantly higher range of DMF values than did the subjects from the custodial institutions who were currently receiving a low fluoride intake.

Students of the effect of fluoride ingestion on the lessening of caries have emphasized particularly the diminution of caries of the anterior teeth.<sup>3</sup> In Table V we have summarized the incidence of carious surfaces in the twelve anterior teeth and in the first molars, the average incidence of each and the proportion which each bears to the total number of DMF surfaces. It will be noted that the number of DMF surfaces in first molar teeth bore an essentially

constant relationship to the total number of DMF lesions, regardless of the geographic subgroup or the presence or absence of mottling. A similar constancy of relationship obtained for caries of the anterior teeth, when the Ankeny subjects were considered separately. Among the institution subjects, however, the incidence of anterior caries was negligible and the average extent minimal among those with mottled enamel, in contrast to notable incidence and extent of anterior caries among those with no mottling. In searching for an explanation of the difference in this regard between the Ankeny and the institution subjects, one must consider the possibility that some areas of enamel dystrophy in the teeth of the Ankeny children may have undergone distintegration, or that fillings may have been placed in some such areas for esthetic reasons.

TABLE V. DISTRIBUTION OF CARIOUS LESIONS BETWEEN ANTERIOR AND POSTERIOR TEETH

	SUBJECTS FROM STATE INSTITUTIONS		SUBJECTS FROM ANKENY HIGH SCHOOL	
	MOTTLING PRESENT	MOTTLING ABSENT	MOTTLING PRESENT	MOTTLING ABSENT
Total number of subjects	77	146	50	35
Proportion of subjects who had caries in anterior teeth	13%	89%	52%	54%
Number of subjects with caries of anterior teeth	10	130	26	19
Total number of DMF surfaces in anterior teeth	18	474	70	51
Average number of anterior DMF surfaces for each subject having anterior caries	1.8	3.6	2.7	2.7
Number of DMF surfaces in all teeth	1,065	2,489	446	522
Percentage of DMF surfaces found in anterior teeth	2%	19%	16%	10%
Total number of DMF surfaces in first permanent molars	556	1,160	209	231
Average number of first molar DMF surfaces for each subject	7.2	8.0	4.2	6.6
Percentage of DMF surfaces found in first permanent molars	48%	47%	47%	44%
Percentage of DMF surfaces found in other posterior teeth (by difference)	50%	34%	37%	44%

The values for anterior caries may be compared with the values found by Knutson, Klein, and Palmer<sup>9</sup> for the elementary school children of Hagerstown. In these children, who ranged in age from 6 to 15 years, caries of the twelve anterior permanent teeth accounted for 10 per cent of all DMF surfaces, and lesions of the first permanent molars accounted for 78 per cent of the total. Obviously direct comparison between these values and the ones herein reported cannot be made, because different values would be expected if Knutson, Klein, and Palmer's values were limited to children in their teen years.

In view of the prevalent opinion that the salivary content of *L. acidophilus* may serve as an index of caries activity or may relate to the rate of caries progression, it seemed worth while to learn whether parallelism could be demonstrated between the *L. acidophilus* counts of these subjects and the presence or absence of mottled enamel. The data are presented in Table VI. At the occasion of the dental examination, saliva samples were collected and these were analyzed by the bacteriologic division of the State Hygienic Laboratories by a

TABLE VI. COMPARISON OF RANGE OF LACTOBACILLUS ACIDOPHILUS COUNTS FROM SALIVA IN TERMS OF THE PRESENCE OR ABSENCE OF MOTTLED ENAMEL IN EACH SUBJECT'S MOUTH

GROUP OF SUBJECTS	MOTTLING PRESENT		MOTTLING ABSENT	
	ANKENY SCHOOL CHILDREN	INSTITUTIONALIZED CHILDREN	ANKENY SCHOOL CHILDREN	INSTITUTIONALIZED CHILDREN
Number of subjects tested	44	57	26	135
<i>L. acidophilus</i> counts:				
Median	1,000	0	13,000	1,000
Middle one-half of range	0 to 10,000	0 to 20,000	0 to 715,000	0 to 30,000
Total range (millions)	0 to 2.7	0 to 3	0 to 1	0 to 2
Percentage of group with counts of less than 500	50%	56%	32%	46%
Percentage of group with counts exceeding 30,000	30%	26%	38%	24%

technician especially trained to provide that service to the dental profession of the state.

In Table VI distinction has been made between those children whose saliva was free or practically free from *L. acidophilus* (500 organisms or fewer) and those who had many organisms (30,000 or more per cubic centimeters of saliva). Cross-comparison is made between the counts of those with and without mottling, and for those living in a region where current ingestion of significant amounts of fluoride is predictable versus those living in a low fluoride region. From the table it will be noted that little difference is apparent between the contrasted groups; and that if significance is to be ascribed to the differences, the Ankeny group must be considered to have higher counts than do the children from the institutions. There is nothing to indicate that either mottling of enamel or current ingestion of fluoride has, in itself, served to lessen the number of *L. acidophilus* organisms in the saliva.

#### SUMMARY AND CONCLUSIONS

The data from this study support the thesis that the incidence of dental caries is lessened in areas of endemic fluorosis. The findings differ sharply from several reported studies in their quantitative aspects. We found caries of some degree in almost every subject; in many children with mottled enamel and with prolonged fluoride ingestion the incidence of carious tooth surfaces was high. Further, there was no evidence to indicate that the current consumption of water containing submottling amounts of fluoride had lessened caries progress in children whose enamel was free from mottling.

Valuable knowledge will be gained from well-controlled serial studies of caries progression rates in individual subjects, in regions where the concentration of fluorine in domestic water supplies approaches the mottling level. Such studies will be equally valuable whether the fluorine occurs naturally or whether it has been added as an experimental or presumably therapeutic measure. The constancy of therapeutic value remains to be demonstrated, especially as it relates to teeth already erupted. The finding of nonconcordant results in different communities with similar fluoride ingestion makes prediction of results of such studies undependable.



There is no need to conclude from studies thus far reported that teeth undergo decay *primarily* because of inadequacy of fluoride ingestion, or because of lack of fluorine in the physicochemical structure of the tooth. Fluorinization remains a pharmacologic, not a physiologic method for the control of caries. These points should be borne in mind in the conduct of fluorine studies. The ultimate answer to caries control probably will lie in the furtherance of innate physiologic protective agencies rather than through pharmacologic procedures.

## REFERENCES

1. Dean, H. T.: Pub. Health Rep. 53: 1443, 1938.
2. Dean, H. T., Jay, P., Arnold, F. A., Jr., and Elvove, E.: Pub. Health Rep. 56: 365, 1941.
3. Dean, H. T., Jay, P., Arnold, F. A., Jr., and Elvove, E.: Pub. Health Rep. 56: 761, 1941.
4. Dean, H. T., Arnold, F. A., Jr., and Elvove, E.: Pub. Health Rep. 57: 1155, 1942.
5. Arnold, F. A., Jr., Dean, H. T., and Elvove, E.: Pub. Health Rep. 57: 773, 1942.
6. Malherbe, M., and Ockerse, T.: South African J. M. Sc. 9: 75, 1944.
7. Ockerse, T.: South African M. J. 18: 255, 1944.
8. Iowa State Planning Board: Mineral Analyses of the Underground Waters of Iowa, State Printing Board, 1938; additional unpublished data.
9. Knutson, J. W., Klein, H., and Palmer, C. E.: J. Am. Dent. A. 27: 579, 1940.
10. Klein, H., Palmer, C. E., and Knutson, J. W.: Pub. Health Rep. 53: 751, 1938.
11. Klein, H., and Palmer, C. E.: Pub. Health Rep. 55: 187, 1940.

## WILMS' TUMOR

### A REVIEW OF SIXTEEN CASES

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ALL OF the published reports of Wilms' tumors in childhood give a rather poor or hopeless prognosis. The largest reported series is that of Ladd and White<sup>1</sup> in which they had sixty operative cases with fourteen children living at least two years postoperatively, a survival rate of 23.3 per cent. Priestly<sup>2</sup> reported thirty-nine operated cases with six survivals, a survival rate of 15.4 per cent. Kretschmer<sup>3</sup> had twenty-seven pathologically proved cases, twenty-five of whom were operated upon with three survivals, a survival rate of 12 per cent. All other reports give similar statistics of a rather high mortality rate with Ladd and White's series having the highest survival rate.

We wish to report a series of sixteen cases of Wilms' tumor that were treated at the University of Michigan Hospital during the nine-year period from Jan. 1, 1934, to Jan. 1, 1943. Eight of these sixteen children are still living, all of them at least three and one-half years since the institution of treatment.

The Wilms' tumor, adenomyofibrosarcoma or embryonal mixed tumor of the kidney, is the most common renal neoplasm occurring in childhood. Ewing<sup>4</sup> states that the great majority of these tumors occur in the first three years of life and seldom after the tenth year. The present series of cases bears out this observation, for twelve of the patients were under 3 years of age, and fifteen of the sixteen were under 6 years of age. The youngest patient in the group was 6 months old at the time of diagnosis.

It is usually stated that there is no sex predominance in these cases. In our series, eight occurred in females and eight in males.

It is well agreed by most authors that this peculiar neoplasm is a developmental tumor. This has been clearly shown by studies of the embryological anlage of the kidney. The epithelium of the urinary tract is derived from the mesodermal intermediate cell mass, and the convoluted tubules arise from the undifferentiated mesenchyma which appears like cellular connective tissue in which glandular elements are formed. These tissues are similar to the pathologic picture observed in a typical Wilms' tumor; a variety of cell types of the epithelial or connective tissue group. There are usually found within the same tumor acinar or adenomatous cells, sarcomatous tissue, smooth muscle, connective tissue, vascular tissues, and occasionally cartilage, and even bone.

Three of our cases did not entirely conform with the usual pathologic picture. Two of them were diagnosed as adenocarcinomas, one of which might have been a variant of a Wilms' tumor. The third was diagnosed as a tera-

toma. We feel that these patients should be included in this series, for clinically they were indistinguishable from a typical Wilms' tumor. Furthermore, as Kretschmer has pointed out, if complete histologic studies are carried out on these tumors, all of the characteristic cell types will usually be found.

#### SYMPTOMATOLOGY

Except in rare instances these tumors develop silently and their discovery almost invariably is made by the mother or nurse who notices the presence of an abnormal mass in the abdomen of the infant. Hematuria is rare and tends to occur late in the course of the disease. Likewise fever, weight loss, and abdominal pain tend to occur only in those patients who have large tumors or tumors of long standing. For the most part, if the child has intelligent and observant parents who discover the tumor early and seek medical advice at once, the patient, when first seen, will be a well-developed and well-nourished child. The symptoms of our patients are enumerated in Table I. We believe that it is significant that the symptoms of weight loss, pallor, vomiting, and abdominal pain occurred only in the cases where there was a delay in seeking medical attention. Therefore, it can be said that in a large majority of the cases of Wilms' tumor, the first noticeable symptom is that of a painless progressive enlargement of the abdomen, and that other symptoms and signs are most often associated with advanced stages of the disease.

TABLE I

SYMPTOMATOLOGY	
Palpable tumor	16
Fever	6
Abdominal pain	9
Loss of weight	4
Hematuria	2
Frequency	4
Vomiting	4
Irritability	4
Pallor	2

#### DIAGNOSIS

The diagnosis of a Wilms' tumor is not difficult for the physician to make. In a child, usually under 5 years of age, with a history of progressive enlargement of the abdomen and with the finding on physical examination of a firm, nontender, smooth or finely nodular mass which usually fills one-half the abdomen one can quickly make the presumptive diagnosis of a Wilms' tumor. The second most common abdominal tumor in childhood and one which gives the most difficulty in the differential diagnosis is the sympathoblastoma, or neuroblastoma, of the adrenal. Other abdominal masses or tumors that are occasionally seen and must be considered in the differential diagnosis are retroperitoneal sarcoma, leucemic infiltrations of liver and spleen, hydronephrosis, polycystic kidneys, mesenteric cyst, ovarian cyst or neoplasm, tuberculous peritonitis, and fecal impactions.

The diagnosis is usually established by pyelography. Subcutaneous or intravenous injection of diodrast is quite simple and in many instances satis-

factory results are obtained. The use of retrograde pyelography is restricted almost entirely to females because it is a particularly traumatic procedure in male infants. Furthermore, such a procedure requires a general anesthetic and therefore, either subcutaneous or intravenous pyelograms are first attempted. If unsuccessful, and if it is felt that pyelograms are necessary for the diagnosis, the retrograde method is used.



FIG. 1.—Intravenous pyelogram showing distortion of the right kidney pelvis and calices and displacement of the ureter by the tumor mass.

The so-called characteristic pyelographic changes seen in a Wilms' tumor are: (1) *distortion of the renal pelvis and calices*, (2) *displacement of renal pelvis upward, downward, or lateralward, depending on the position of the tumor within the kidney*, and (3) *failure of visualization of the kidney pelvis*. However, it should be remembered that these described changes are not absolutely diagnostic, but merely suggestive of a Wilms' tumor. When no contrast medium can be seen in the pelvis or calices on the affected side, the diagnostician must think of hydronephrosis as well as neoplasm. Twice during the past fifteen years our surgeons have found massive hydronephrosis to be the condition responsible for large renal tumor masses that were operated upon with the presumptive diagnosis of Wilms' tumor.

A procedure formerly used as an aid in the diagnosis but now thrown into discard, is that of aspiration biopsy. It is felt that the risk of setting malignant cells free into the peritoneal cavity as metastatic sites does not

warrant this procedure being carried out. Furthermore, too often the material aspirated is either normal kidney tissue or if there are tumor cells present they are not representative enough to make a clear-cut diagnosis.



Fig. 2—Retrograde pyelogram showing typical distortion of the right kidney, pelvis and calices in a Wilms' tumor. Note the complete displacement of the right kidney into the left half of the abdomen by the tumor mass

#### TREATMENT

Although most authors agree that irradiation and surgical removal of the tumor is the treatment of choice, there is no unanimity of opinion. Ladd and White,<sup>1</sup> in giving an excellent discussion of preoperative irradiation, came to the conclusion that the chance of survival is greater if a policy of immediate nephrectomy is adopted rather than waiting for preoperative irradiation shrinkage of the tumor. Priestly and Broders,<sup>5</sup> on the other hand, took the more widely accepted view that both preoperative and postoperative irradiation is desirable. They recommended surgical removal of the tumor four to six weeks after the institution of irradiation therapy. Postoperative irradiation, in their opinion, should be given over the entire abdomen and thorax. Our series of cases is small and the fact that the treatment has varied from patient to patient makes it impossible for use to draw any conclusions

as to what is the proper form of therapy. However, in recent years we have adopted the following policy in treating these patients: preoperative irradiation is reserved for those cases in which the tumor is so large that operative removal would be technically very difficult, thus minimizing the chances for survival. This naturally means that the majority of the patients receive preoperative irradiation, for, as has already been pointed out, the outstanding feature of this tumor is the enormous size to which it grows before giving rise to any symptoms. Occasionally, however, we do see a patient in which the abdominal enlargement has been noted early and the tumor has not reached



Fig. 3—Retrograde pyelogram showing downward displacement and distortion of the left kidney pelvis and calices.

tremendous proportions, thus making safe surgical procedure feasible. On this type of patient preoperative irradiation is dispensed with and nephrectomy is carried out immediately. Postoperative irradiation was formerly employed only in those patients in whom regional metastases were grossly evident at the time of operation, or if pathologic study of the regional lymph nodes showed metastatic involvement. However, we have now adopted the policy of giving all patients postoperative irradiation. We have made this change in policy because three of the eight living patients very definitely owe their survival to irradiation therapy. As such, we now feel that every patient should have the benefit of possible lifesaving postoperative irradiation.

In view of possible errors in diagnosis, we have operated upon all tumors of the kidney, regardless of size or evidences of local fixation, provided the chest is free from roentgen evidences of metastases. As previously noted, massive hydronephrosis was encountered in two such instances. In each case preoperative irradiation had failed to shrink the tumor mass and operation was performed with the avowed hope that an error in diagnosis would be thereby disclosed.

#### OPERATIVE TECHNIQUE

The technique of operation that has been employed in all of our cases has consisted of the standard oblique flank incision extended rather long anteriorly to permit opening the peritoneum for the purpose of exploration for local extension of the neoplasm. It is of interest in this connection that one of the survivors in the present series of cases (eleven-year survival) had peritoneal infiltration from the upper pole of the neoplasm that necessitated the excision of an area of peritoneum 4 by 4 inches in diameter along with the tumor. We have routinely approached the pedicle of the kidney from the back, having never developed a satisfactory technique of transperitoneal approach to this structure. Hilar lymph nodes are removed for biopsy when adenopathy is observed.

#### RESULTS OF TREATMENT

Our series consists of sixteen patients in whom the diagnosis of a Wilms' tumor was confirmed by pathologic study. Of these sixteen children, eight are still living for a period of time ranging from three and one-half to eleven and one-half years since the institution of treatment. Table II summarizes the treatment of the eight survivors.

TABLE II. SURVIVALS

PATIENT	SEX	AGE	TREATMENT	SURVIVAL (YR.)
1	M	5 yr.	Nephrectomy	11½
2	M	4 yr.	Nephrectomy	11
3	F	3 yr.	Nephrectomy; postoperative irradiation	11
4	F	3 yr.	Irradiation	10
5	F	2 yr.	Preoperative irradiation; nephrectomy	8½
6	F	10 mo.	Preoperative irradiation; nephrectomy	8
7	M	4 yr.	Nephrectomy; postoperative irradiation	4
8	F	10 mo.	Nephrectomy	3½

It is of particular interest to note that of the eight children apparently cured, only seven had nephrectomies. The survivor who was not operated upon was first seen here in 1933, at the age of 14 months with idiopathic hydrocephalus. She was next seen in March, 1935, with the new complaint of abdominal enlargement; the hydrocephalus had since become arrested. Physical examination at that time revealed a huge finely nodular mass occupying the entire right half of the abdomen. An intravenous pyelogram failed to show any visualization of the right renal pelvis. An aspiration punch biopsy was sufficiently diagnostic to make a clear-cut diagnosis of Wilms' tumor. Chest x-rays showed a right pleural effusion interpreted as being due to meta-

static lesions in the lung. Therefore, the tumor was considered to be inoperable and she was given palliative irradiation therapy over the right abdomen and right chest. She received a total of 1,800 r. in divided doses over a period of two weeks' time. She was not seen again until 1939, when an examination revealed no evidence of any abdominal mass and the chest was clear by x-ray. She was last examined by us in October, 1945, and was free from evidences of neoplasm at that time, ten years following the original diagnosis. Another intravenous pyelogram done at this time still showed nonvisualization of the right kidney pelvis and normal visualization of the left kidney pelvis and calices. This must, therefore, be classified as a possible cure of an embryoma of the kidney by x-ray therapy alone.

Twelve of the sixteen patients had nephrectomies. Seven of these children have lived long enough postoperatively to be considered cures by the standards set up by most authors.

Two of these patients, at operation, had gross evidence of retroperitoneal extension of the tumor. They were given postoperative irradiation and the fact that they are still living shows adequately the value of this procedure.

With one exception, all of the five patients who had nephrectomies and that have since died, showed evidence of metastases within six months postoperatively. However, the one exception lived three and one-half years before showing recurrence of the tumor. This child should be kept in mind when evaluating postoperative survival statistics.

Operation was denied four of the sixteen patients, either because of pulmonary metastases, or because they were in such poor condition that they were considered hopeless operative risks. One of these has already been discussed, the child who has survived ten years following x-ray therapy alone. All the remaining three patients in this group had a typical history and physical findings of a Wilms' tumor, and the pathologic study was made by punch biopsy. These three died within five months from the time they were first seen here.

Throughout this same nine-year period there was a total of twenty-seven cases observed, upon which a presumptive clinical diagnosis of Wilms' tumor was made, but of this group only the herein discussed sixteen patients had the diagnosis confirmed by microscopic examination. The remaining eleven had no pathologic diagnosis made for various reasons. Five of them had a large abdominal tumor with distortion of the renal pelvis by pyelography, but had metastatic lesions in the lungs by x-ray and were therefore deemed inoperable. These five patients received palliative x-ray therapy and all subsequently died. Two patients had clinical evidence of a Wilms' tumor and operation was advised but was refused by the parents. Both of these children are dead. Three children had the presumptive diagnosis made here, but were operated on elsewhere and we were unable to obtain pathologic material from these tumors for study. Two of these patients are still living and well, seven years and five years postoperatively. The eleventh patient was seen in 1934, and the tumor was said to be too large for operative removal. We do not feel



PATIENT	AGE	SEX	DATE	CHIEF COMPLAINT	PREOP- ERATIVE IRRADI- ATION	NEPHREC- TOMY	POSTOP- ERATIVE IRRADI- ATION	COURSE	PATHOLOGY	COMMENT
S. V.	5 yr.	M	1/29/34	Abdominal pain	0	2/ 2/34	0	Alive 11½ yr.	Operative specimen Wilms' tumor	
D. M.	4 yr.	M	7/26/34	Bloody urine	0	8/ 1/34	0	Alive 11 yr.	Operative specimen adenocarcinoma	
A. H.	3 yr.	F	8/16/34	Large abdomen	0	9/ 5/34	Yes	Alive 11 yr.	Operative specimen Wilms' tumor	At operation retroperitoneal infiltration from superior pole of tumor
N. B.	10 yr.	F	10/ 9/34	Large abdomen	0	10/13/34	Yes	Dead 1/10/34 27 mo.	Operative specimen adenocarcinoma ? variant Wilms'	At operation peritoneal at- tachment; 6 mo. postop- ative chest metastasis by x-ray
D. C.	6 mo.	M	12/ 3/34	Abdominal mass	0	0	0	Dead 1/5/35 1 mo.	Punch biopsy Wilms' tumor	Inoperable because of poor condition of patient
S. B.	3 yr.	F	3/ 4/35	Abdominal growth	Yes	0	0	Alive 10 yr.	Punch biopsy Wilms' tumor	Inoperable because of chest metastases, therefore only given irradiation
B. G.	3 yr.	F	3/29/35	Large abdomen	Yes	0	0	Dead 5/24/35 2 mo.	Autopsy Wilms' tumor	Inoperable abdominal metas- tases
J. N.	21 mo.	M	5/11/35	Abdominal "swell- ing"	Yes	6/ 6/35	0	Dead 3/20/40 4 yr. 9 mo.	Operative specimen Wilms' tumor	In good condition for 3½ yr. postoperative, then ab- dominal metastases found
H. F.	14 mo.	M	1/24/36	Abdominal tumor	Yes	2/28/36	Yes	Dead 7/26/36	Operative specimen Wilms' tumor	At operation retroperitoneal extension
J. B.	2 yr.	F	2/15/36	Large abdomen	Yes	4/13/36	0	Alive 8 yr.	Operative specimen Wilms' tumor	
D. S.	15 mo.	M	6/ 3/36	Abdominal mass	Yes	0	0	Dead 11/20/36 5 mo.	Punch biopsy Wilms' tumor	Inoperable because of poor condition of patient
S. G.	10 mo.	F	9/24/36	Abdominal tumor	Yes	12/30/36	0	Alive 8½ yr.	Operative specimen teratoma	
S. M.	4 yr.	M	11/24/40	Large abdomen	0	12/ 4/40	Yes	Alive 4 yr.	Operative specimen Wilms' tumor	At operation many large in- volved nodes left; clasped as hopeless
S. P.	10 mo.	F	4/23/42	Large abdomen	0	5/ 7/42	0	Alive 3 yr.	Operative specimen Wilms' tumor	
T. G.	3 yr.	M	8/28/42	Abdominal mass	0	9/12/42	0	Dead 2/6/43 5 mo.	Operative specimen Wilms' tumor	
S. W.	3 yr.	F	12/ 7/42	Large abdomen	0	12/14/42	0	Dead 2/10/43 2 mo.	Operative specimen Wilms' tumor	Developed chest metastases two weeks after operation

that these patients should be included in a statistical analysis for they were never proved by pathologic study.

#### SUMMARY

1. A series of sixteen children with Wilms' tumor of the kidney is presented.

2. Twelve of the patients had nephrectomy and seven of these are alive, three and one-half to eleven and one-half years postoperatively, a survival rate of 58.4 per cent.

3. Two of the nephrectomized patients who had retroperitoneal infiltration with neoplasm and were given postoperative irradiation have survived four and eleven years without clinical evidences of recurrence.

4. One child, considered inoperable because of questionable chest metastases, was treated by x-ray alone. She has survived ten years and today appears well.

5. Thus, among the eight living patients in the present series it is our belief that three owe their survival to irradiation therapy and we are therefore inevitably led to the conclusion that postoperative irradiation is indicated in all patients.

#### REFERENCES

1. Ladd, W. E., and White, R. R.: *J. A. M. A.* 117: 1858, 1941.
2. Priestley, J. T.: *J. A. M. A.* 113: 902, 1939.
3. Kretschmer, H. L.: *J. Urol.* 39: 250, 1938.
4. Ewing, J.: *Neoplastic Diseases*, Philadelphia, 1920, W. B. Saunders Company.
5. Priestley, J. T., and Broders, A. C.: *J. Urol.* 33: 544, 1935.

## A DEVELOPMENTAL GRAPH FOR THE FIRST YEAR OF LIFE

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THIS developmental graph is presented in the hope that it will help physicians to follow, with the minimal expenditure of time and effort, the neuromuscular growth of infants under their care and that these steps may be used as an index of the child's maturity.

Since growth follows a regular pattern, the sequence of the steps is established and progressive. This enables one to demonstrate to the mother, each time she comes for advice, what her child will be doing next in his progress.

While the sequence is rigid, each child has his own rate of growth, which reflects his own individuality as well as his maturity. However, the appearance of these emerging abilities may be modified somewhat by the effects of environment.

We followed the development of 215 normal infants from birth to the early part of their second year. The parents of these infants came from all strata of society in Rochester, Minn., which, however, has a larger proportion of professional people than is usual.

We explained to each mother how her infant's behavior would follow the sequence of growth and advised her to encourage her baby to use each ability as it appeared. Since we were to record the time of onset of these various accomplishments, this information was obtained by testing the infants at monthly intervals and instructing the mothers to watch for the achievements not so easily elicited in the clinic. The latter method is subject to the inaccuracy of lay observation but does allow the infant to be observed in his natural environment by an interested person.

The more evident steps in neuromuscular growth were chosen. Some of these have been used previously<sup>1</sup> to make parents conscious of the stereotyped progress of growth. The selected steps were:

1. Smile—the baby begins to smile in response to an adult or to his voice.
2. Vocal—the infant utters such sounds as “ah,” “eh,” and “uh” spontaneously or on stimulation.
3. Head control—when the infant is lifted by his hands from the supine to the sitting position, the head does not lag but is supported by the anterior muscles of the neck.
4. Hand control—when a toy is dangled in the midline above his chest, the infant is able to close in on the toy with one or both hands and to grasp it.
5. Roll—the baby makes a complete roll from back to abdomen.
6. Sit—the baby sits alone for several moments.
7. Crawl—the baby is able to move across the room or pen toward some distant object; this may be accomplished by rolling over and over, pushing

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himself along on his stomach or back, or by any individual modification of progression.

8. Prehension—this is the bringing together of the thumb and index finger to pick up a small object. This can be tested with a bright-colored button.

9. Pull up—the infant pulls himself to a standing position.

10. Walk with support—the infant walks by holding to his playpen, a piece of furniture, or an adult.

11. Stand alone—without any support, the infant stands for several moments.

12. Walk alone—the infant takes several steps alone.

While our records aimed to record the onset of these achievements in infancy, many of the statements in the literature indicate the age of achievement of the perfected act; hence, they will record a somewhat later age. In previous reports there is a wide variation in the number of infants observed, their selection, the methods of testing them, and the definition of the various levels of development.

It is generally stated that the first voluntary behavior is smiling in response to the mother's voice, which occurred in our series at the average age of 0.9 month. Chaillé<sup>2</sup> stated that after 3 weeks of age many babies begin to smile. Preyer<sup>3</sup> observed a smile on his son's face during the fourth week (0.9 month). Sixty per cent of babies smile socially at one month of age according to Linfert and Hierholzer,<sup>4</sup> while others have recorded this as an accomplishment at 1.4 months<sup>5, 6</sup> and at 2 months.<sup>7-10</sup>

Morgan and Morgan<sup>9</sup> found that one-half of the babies were cooing at 6 weeks (1.4 months), as was also found by Gesell, Thompson, and Amatruda,<sup>6</sup> and Bayley.<sup>5</sup> The average infant in our group uttered sounds, such as "uh" and "ah," at 1.7 months. Other authors<sup>3, 7, 8, 11</sup> have reported vocalization at 2 months.

When the infant is raised from the supine to the sitting position, the head will lag slightly at 12 weeks (2.8 months) according to Gesell and associates and at 16 weeks (3.7 months) according to Amatruda.<sup>12</sup> We found, on the average, the baby was able to control his head at 2.9 months. Other authors have stated that the head could be held erect and steady at 3 months,<sup>2, 11</sup> and at 4 months.<sup>4</sup>

Bühler<sup>7</sup> expressed the belief that the ability of the infant to reach for and grasp a toy is the best index of normal activity in a 4-month-old child. This is the age at which our average infant attained this achievement. Gesell<sup>13</sup> and Hetzer and Wolf<sup>8</sup> have observed reaching movements in infants at this age and stated that the infants may close in on the object and grasp it, while some<sup>10, 14, 15</sup> have seen this achievement first during the fifth month.

In our series the mothers first observed their infants to roll from back to stomach at an average age of 5.1 months, while Shinn<sup>10</sup> saw her niece do this at 24 weeks (5.5 months). Gesell<sup>16</sup> stated that a few infants may roll from back to stomach as early as 4 months but that this is a usual feat at 6 months. Bühler reported this ability at 6 months, Shirley<sup>15</sup> at 29 weeks (6.7 months), and Hetzer and Wolf at 7 months.

The average infant in our group was sitting alone for several minutes at 6.2 months. Sitting alone, at least briefly, has been reported at 25 weeks (5.8 months),<sup>10</sup> 6 months,<sup>2, 14</sup> and 7 months.<sup>13, 15</sup>

By many diverse means our average infant began "going places" on the floor at 7.3 months. Bühler<sup>7</sup> and others<sup>2, 8</sup> reported that infants are able to move toward a desired object at 7 months, while some consider crawling at 8 months<sup>13</sup> and 8.5 months<sup>15</sup> an achievement.

Our infants started to pick up objects with thumb and forefinger at an average age of 8.1 months. Gesell<sup>13</sup> stated that the 9-month-old infant can bring the thumb and forefinger together deftly in a plucking movement and that this movement is highly characteristic of that age. Bayley listed this as an accomplishment at 9.3 months.

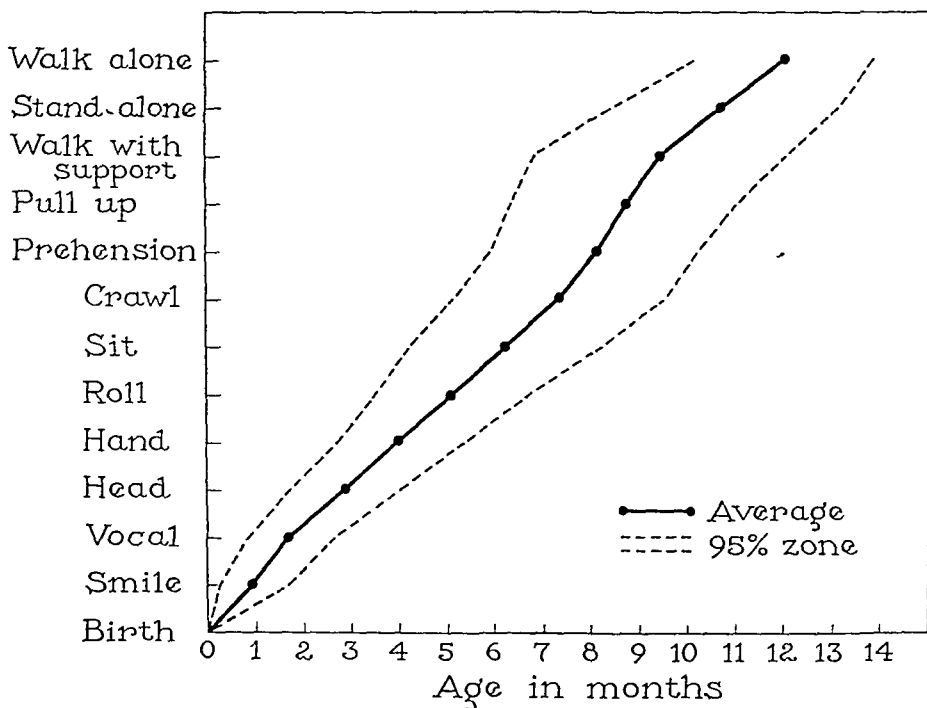


Fig. 1.—A developmental graph for the first year of life shows the average age for the achievements selected and the zone in which 95 per cent of the infants' developmental graphs fell.

Shinn reported that her niece pulled herself to a standing position at 33 weeks (7.6 months) and Bühler observed the first attempts of an infant to raise himself to a standing position at 8 months, while our infants did this at the average age of 8.7 months. Others have reported this at 9 months<sup>2, 13</sup> and 10 months.<sup>8, 15</sup>

Infants have been seen to walk with help at 9 months,<sup>6, 7</sup> 42 weeks (9.7 months),<sup>15</sup> and 49 weeks (11.3 months),<sup>10</sup> but Gesell<sup>13</sup> listed this as an achievement for those 12 months of age. The average child in our series walked with help at 9.5 months.

Shinn's niece stood alone on the three hundred and sixteenth day (10.4 months). Our average child was observed to stand alone for several moments at 10.7 months, but Gesell and Thompson have this as a momentary achievement in their age group at 56 weeks (12.9 months).

Our average child as well as Shinn's niece and Chaillé's group of children succeeded in walking alone at 12 months of age. Shirley expressed the belief that this may occur between 11.5 and 17.5 months, while 77 per cent of McGraw's<sup>17</sup> series were walking independently by 14 months and the median child of Gesell's<sup>13</sup> group walked at 15 months.

The average ages of these developmental steps are shown in Fig. 1. There was no difference between the rate of the boys and that of the girls. The course of the more rapidly developing infants and of the slower ones followed the average graph but at earlier and later ages, respectively.

Our results in this study show the age of walking alone to be accelerated about two months as compared with the generally accepted standards. Inasmuch as our group forms a fairly representative sampling of an average American city we find it hard to account for this discrepancy. It may be due to the fact that our mothers were instructed to foster rather than to oppose the steps of growth. Possibly the emotional freedom thus produced had an influence on the early postural achievements of the group.

#### SUMMARY

Twelve developmental steps of neuromuscular growth were chosen for study in an unselected group of 215 infants observed at a well baby clinic. Observations of the age of attainment of these steps were made and a graph depicting the average curve and the variation is presented. In our group walking alone appeared accelerated somewhat as compared with the generally accepted standard time.

#### REFERENCES

1. Aldrich, C. A.: *J. PEDIAT.* 20: 272, 1942.
2. Chaillé, S. E.: *New Orleans M. & S. J.* 14: 893, 1886-1887.
3. Preyer, W.: *Mental Development in the Child* (Translated by H. W. Brown), New York, 1893, D. Appleton and Company.
4. Linfert, H. E., and Hierholzer, H. M.: *Stud. Psychol. & Psychiat.* 1: 1, 1926-1928.
5. Bayley, N.: *Mental Growth During the First Three Years*, In Barker, R. G., Kounin, J. S., and Wright, H. F.: *Child Behavior and Development; a Course of Representative Studies*, ed. 1, New York, 1943, McGraw-Hill Book Company, Inc., chap. 6, pp. 87-105.
6. Gesell, A., Thompson, H., and Amatruda, C. S.: *The Psychology of Early Growth; Including Norms of Infant Behavior and a Method of Genetic Analysis*, New York, 1938, The Macmillan Company.
7. Bühler, C.: *The first year of life* (Translated by Pearl Greenberg and Rowena Ripin), New York, 1930, The John Day Company, Inc.
8. Hetzer, H., and Wolf, K.: *Ztschr. f. Psychol. u. Physiol. d. Sinnesorg.* (Abt. 1) 107: 62, 1928.
9. Morgan, S. S., and Morgan, J. J. B.: *J. PEDIAT.* 25: 168, 1944.
10. Shinn, M. W.: *Notes on the Development of a Child*, vol. 1, Berkeley, 1899, University of California Press, pts. 3-4.
11. Cattell, P.: *The Measurement of Intelligence of Infants and Young Children*, New York, 1940, The Psychological Corporation.
12. Amatruda, C. S.: *J. PEDIAT.* 20: 265, 1942.

13. Gesell, A.: *Infancy and Human Growth*, New York, 1928, The Macmillan Company.
14. Halverson, H. M.: *The Development of Prehension in Infants*, In Barker, R. G., Kounin, J. S., and Wright, H. F.: *Child Behavior and Development; a Course of Representative Studies*, ed. 1, New York, 1943, McGraw-Hill Book Company, Inc., chap. 4, pp. 49-65.
15. Shirley, M. M.: *The First Two Years: A Study of Twenty-Five Babies, Volume I: Postural and Locomotor Development*, Minneapolis, 1931, The University of Minnesota Press.
16. Gesell, A. L.: *The Mental Growth of Pre-school Child; a Psychological Outline of Normal Development From Birth to the Sixth Year, Including a System of Developmental Diagnosis*, New York, 1925, The Macmillan Company.
17. McGraw, M. B.: *J. PEDIAT.* 17: 747, 1940.

## "VIRUS PNEUMONIA"

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THE much abused and inappropriate term virus pneumonia obviously denotes a form of pneumonia induced by a virus. A number of different viruses are in fact capable of causing pneumonia in birds and animals but may be harbored in susceptible species with or without apparent disease. Among these, viruses of the psittacosis-lymphogranuloma or ornithosis group are also capable of causing pneumonia in man.<sup>1, 2</sup> In many cases of pneumonia attributable to viruses included in this group, it is possible to trace the source of infection to birds such as parrots, parakeets, or pigeons. Although numerous instances of human ornithosis have been reported, the incidence of this variety of pneumonia in human beings is probably low.<sup>2, 3, 4, 5</sup>

Still other viruses, some of which are capable of causing pneumonia in animals, have been suspected to be causative also of pneumonia in man.<sup>6</sup> Among these are the viruses of influenza, lymphocytic choriomeningitis, and measles. In human infections with each of these agents symptoms referable to the respiratory tract are common. It remains to be established, however, whether in man the pneumonia which may occur during infection with any of these viruses is caused by the virus itself or results from the presence of some other agent which acts as a concomitant or secondary invader.

Certain rickettsial infections are also associated with pneumonia. *Rickettsia burneti* or *diaporica* is the causative agent of so-called Q fever, a form of pneumonia which was first recognized among meat handlers in Queensland, Australia, and has occurred in laboratory workers who have studied the agent. Reports concerning the occurrence, clinical manifestations, and etiology of Q fever have been reviewed recently.<sup>6</sup> It is debatable whether pneumonia which may occur in the course of other rickettsial infections of human beings is attributable directly to the rickettsiae.

It may be said of all of these agents, whether known or suspected to be capable of inducing pneumonia in human beings, that none of them was responsible for the vast majority of cases which have been grouped together as instances of so-called virus pneumonia.

Virus pneumonia, acute pneumonitis, or primary atypical pneumonia are a few of many terms used to designate an acute respiratory disease which during the past twelve years has become an increasingly familiar *clinical* syndrome. Early reports calling attention to this form of pneumonia were followed by numerous other publications which have been reviewed recently.<sup>7-11</sup>

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The illness is usually characterized by a gradual onset, fever, cough, headache, relative bradycardia, evidence of pneumonia more apparent by x-ray than by physical examination, and a normal or only slightly elevated leucocyte count. Patients frequently develop in their serum cold agglutinins for human erythrocytes. Convalescence may be protracted, complications are uncommon, and the illness almost invariably is followed by complete recovery.

Although probably not a new disease, an increasing awareness of its occurrence during the past decade has suggested that this form of pneumonia may have increased in prevalence. In the Armed Forces during World War II, it was encountered more frequently than bacterial pneumonias. The illness has a widespread geographic distribution, affects all age groups but most frequently young adults, and occurs throughout the year, but especially in those seasons when colds and other undifferentiated forms of respiratory infections are most prevalent. Its scattered occurrence in communities where milder varieties of respiratory disease are current has been noted repeatedly and has suggested that this form of pneumonia may be a more severe manifestation of certain common respiratory infections of undetermined etiology. The results of epidemiological and experimental studies have provided some evidence in support of this view.<sup>3, 12</sup> It appears that the incubation period may vary from one to three weeks but is usually about two weeks.

The term primary atypical pneumonia although not unobjectionable has been useful in distinguishing this form of pneumonia from clinically similar illnesses attributable to known infectious agents including bacteria, fungi, rickettsiae, and viruses. Although primary atypical pneumonia is generally considered to be of nonbacterial origin, the failure to incriminate pathogenic bacteria does not warrant the assumption that the illness is therefore caused by a virus. Extensive and painstaking efforts to determine the causative agent have not as yet resulted in completely satisfactory conclusions. It is not possible here to review all of the studies of primary atypical pneumonia, but an effort will be made to present the salient clinical features of the illness and to indicate the present status of knowledge concerning the etiology of this syndrome.

The clinical manifestations of primary atypical pneumonia vary considerably in individual patients; those observed in 106 young adults studied at the Hospital of The Rockefeller Institute<sup>4</sup> are representative and similar to those described in other reports.

The onset of illness in approximately 75 per cent of patients is gradual and ill-defined. Initially the symptoms are frequently those of a cold or grippe. Malaise, fever, headache, and cough are common early complaints; chilly sensations may occur on more than one occasion, frank chills are exceptional. Coughing frequently accentuates substernal discomfort or pain; the sharp lateral chest pain so often associated with pleuritis is uncommon. The cough in this illness is usually dry at first, but in most instances, becomes productive of mucopurulent sputum, which may be copious, and may at times be blood-tinged. Rusty or frankly bloody sputum is only occasionally observed.

Fever is almost invariably present during the acute phase of illness, but the pulse and respiratory rates are generally normal or only slightly elevated,

a helpful feature in differentiating this disease from the common bacterial pneumonias. The patients usually do not appear as ill as the fever might lead one to expect. Abnormal pulmonary signs for the first few days are minimal or absent. Diminution of breath sounds over an affected area is often the first alteration noted. Scattered inconstant fine râles, and slight reduction in percussion resonance may follow. Later, during resolution, râles are more frequently heard and may be moist or coarse. The transmission of voice sounds is usually unaltered; signs of true consolidation are infrequent. Abnormal physical signs in the lungs when present may vary markedly within very short intervals. Râles may persist after x-ray evidence of pneumonia has disappeared. Except in the most severely ill patients, or for brief intervals associated with paroxysms of coughing, dyspnea and cyanosis are not seen.

X-ray films of the lungs usually reveal more extensive pulmonary involvement than would be anticipated from the results of physical examination and may provide the only objective evidence for making a diagnosis of pneumonia. The site of pneumonia is most frequently in the lower lobes with about the same incidence for each side. Consolidation in an upper or the middle lobe is usually, but not always associated with consolidation elsewhere. Involvement of more than one lobe occurs in approximately 50 per cent of patients.

Pulmonary lesions as viewed in x-ray films show extraordinary variations in density as well as distribution. In most instances consolidation first appears and is most dense at the hilum, spreading and becoming less dense toward the periphery of the lung. The affected areas are frequently mottled in appearance and the borders are usually irregular and ill-defined. Resolution occurs in several ways, but in most instances clearing proceeds from the periphery of the lung toward the hilum, sometimes leaving residual accentuation of the bronchovascular markings of questionable significance.

Only rarely is the density or extent of pulmonary consolidation in a given lobe comparable to that seen in characteristic films of patients with lobar pneumonia. Infiltration radiating from the hilum and involvement of an upper lobe may resemble tuberculous lesions, and, occasionally, the presence of small abscess cavities is suggested. Other shadows, especially in the lower lobes, may arouse a suspicion of bronchiectasis. The relative rapidity with which abnormal x-ray findings usually disappear is of particular value in excluding a diagnosis of chronic pulmonary disease. It should be emphasized, however, that a diagnosis of primary atypical pneumonia cannot be made on the basis of x-ray evidence exclusively, but only in conjunction with other findings, both clinical and laboratory.

The leucocyte count on admission and at intervals thereafter is usually normal or only slightly elevated. This is another helpful feature in distinguishing primary atypical pneumonia from the bacterial pneumonias in which leucocytosis characteristically occurs. Elevation of the erythrocyte sedimentation rate is usual in the acute phase of illness and persists on the average for four weeks. Electrocardiograms, urinalyses, and biochemical assays of blood and urine usually reveal no significant abnormalities.

Cultures of the blood show no bacterial growth. The bacterial species found in ordinary examinations and cultures of the nose, throat, and sputum are generally similar to those encountered in the respiratory passages of normal human beings.

Sera obtained from patients studied at the Hospital of The Rockefeller Institute<sup>4</sup> were tested for the presence of antibodies against viruses known or thought to be capable of inducing respiratory disease in man. These included influenza A, influenza B, and swine influenza viruses, as well as the viruses of psittacosis and lymphocytic choriomeningitis. The results indicated conclusively that none of these viruses was causally related to primary atypical pneumonia in the group of patients studied.

In the course of these investigations it was found that certain patients with primary atypical pneumonia develop in their serum the capacity to fix complement with a variety of apparently unrelated antigens prepared from normal or infected tissues of several different species.<sup>13</sup> This observation is pertinent in interpreting the results of complement fixation tests with serum from patients with atypical pneumonia.

The course of the illness is extremely variable. In the series already cited<sup>4</sup> all of the patients recovered. The average duration of fever was 10 days and of pneumonia, on the basis of physical signs, 13 days with a range of 0 to 41 days in both categories. The average duration of pneumonia as determined by serial x-ray films was 14 days with a range of 3 to 41 days. Complications were infrequent and usually not severe. These included pleuritis, sinusitis, otitis media, and stomatitis. The development of bronchiectasis following atypical pneumonia has been reported.<sup>14</sup> The general incidence of fatalities has averaged considerably less than 1 per cent.

The treatment of primary atypical pneumonia does not differ from the symptomatic and supportive therapy commonly used in other forms of pneumonia. Alleviation of headache and measures to relieve cough without entirely suppressing it are usually the chief requirements. Treatment with either sulfonamide drugs or penicillin has not been found to be effective.

The published reports on the occurrence of cold hemagglutinins in primary atypical pneumonia have been reviewed recently.<sup>15</sup> All investigators of this phenomenon are in agreement that during the course of this illness numerous patients develop in their serum the capacity to agglutinate human erythrocytes in the cold. Maximum cold hemagglutination titers are usually attained between the first and second week. Group 0 erythrocytes are used in these tests because they lack A and B isoagglutinogens. Suspensions of washed erythrocytes in 2 per cent concentration are mixed in equal volumes with serial dilutions of serum, and agglutination is read after the mixtures have stood overnight in the refrigerator.

The frequency with which significant titers of cold hemagglutinins were found in patients with primary atypical pneumonia has varied considerably in different published studies and appears to be influenced by several factors, particularly the severity of illness, the manner in which the serum is separated, and the concentration of red blood cells used in the test. The incidence and

titer of cold hemagglutinins have generally been higher in the serum of more severely ill patients. Cold hemagglutinins may be completely removed from serum by absorption with human red blood cells in the cold. Therefore, unless the serum to be tested is separated from the clot prior to refrigeration, cold hemagglutinins present may be reduced in titer or removed entirely. In tests carried out with concentrations of red blood cells of less than 2 per cent higher titers are obtained, but reactions with normal serum or serum from patients with other illnesses occur more frequently.

From an analysis<sup>15</sup> of published investigations of cold hemagglutinins in cases of primary atypical pneumonia and regarding 1:40 as the minimal significant titer, it appears that approximately 50 per cent of patients develop this unusual and unexplained serologic property. Under similar conditions the occurrence of cold hemagglutinins in control sera is probably less than 5 per cent, and in serum from patients with other common illnesses a rise in titer is almost never seen.

In the course of studies at the Hospital of The Rockefeller Institute a nonhemolytic streptococcus, designated streptococcus MG, was first isolated from the lungs of a patient who died elsewhere of atypical pneumonia. Subsequently<sup>16, 17</sup> by means of specially devised selective media the same microorganism was recovered from the lungs in five other fatal cases and from sputa or nasopharyngeal washings of fifty-three patients. Although sometimes found in the respiratory passages of human beings who are healthy or ill with other forms of respiratory disease, streptococcus MG appears to occur most frequently in patients with primary atypical pneumonia.

All strains of streptococcus MG isolated to date belong to a single serologic type.<sup>16, 17</sup> Present evidence indicates that streptococcus MG represents a distinct and previously undifferentiated species of nonhemolytic streptococcus. Streptococcus MG is infectious in high dilution in chick embryos but not in any other species tested. This microorganism possesses a capsular polysaccharide which is responsible for the type specific serologic reactions obtained with it. Injection of streptococcus MG into animals results in the production of antibodies against both the specific capsular polysaccharide antigen and another somatic antigen present in the organism.

The capsular polysaccharide when injected into rabbits fails to stimulate antibodies, but in man results in the development of antibodies capable of agglutinating the streptococcus and precipitating the capsular polysaccharide. Individuals whose serum contains antibodies against streptococcus MG sometimes show dermal reactions to injections of capsular polysaccharide. It has been found and confirmed by other workers<sup>3, 18, 19</sup> that during the course of primary atypical pneumonia many patients develop antibodies against streptococcus MG. This can be demonstrated by agglutination tests with the organism or in certain instances by precipitation tests with the capsular polysaccharide. Moreover, it can be shown that these patients develop antibodies against both the specific capsular polysaccharide antigen and a somatic antigen of the microorganism.

In summarizing the published serologic data,<sup>15</sup> and regarding a titer of 1:20 or more as significant, approximately 50 per cent of patients with primary

atypical pneumonia develop agglutinins for streptococcus MG whereas in normal persons or patients with other disease such antibodies are found in 5 per cent or less. Appreciable increments in agglutination titer apparently are rare during illnesses other than primary atypical pneumonia. It will be recalled that the occurrence of cold hemagglutinins is similar. The highest incidence of agglutinins for streptococcus MG occurs between the fourth and sixth weeks of illness and in most instances agglutinins are first detected at the time of defervescence or later during convalescence. Using duration of fever and of pneumonia as criteria for severity of illness it has been noted that there is a positive correlation between the severity of illness and the incidence of streptococcal agglutinins as well as the agglutination titer.<sup>4</sup> In this respect there is also a similarity to the occurrence of cold hemagglutinins. Cold hemagglutinins occur predominantly, but not exclusively in sera of patients possessing agglutinins against streptococcus MG, although each may occur in the absence of the other. It can be shown, however, by cross absorption experiments that the two phenomena are independent of each other and can be clearly differentiated.

During the past several years numerous reports have been published by different groups of investigators indicating the recovery of various infectious agents from patients with primary atypical pneumonia. Most of these reports have been cited repeatedly by various authors in reviews.<sup>3, 4, 7, 8-11</sup> At present there is no published confirmation or additional evidence available to warrant the conclusion that any one of the agents described is etiologically responsible for the majority of cases of primary atypical pneumonia. Latent viruses harbored by apparently normal animals used in transmission experiments have been encountered frequently and have seriously complicated efforts to recover an infectious agent from human materials.

The assumption that primary atypical pneumonia may result from infection with a filtrable agent has been supported by evidence presented recently by two different groups of investigators. Eaton and his associates<sup>20</sup> have reported the recovery from several patients of a virus transmissible in chick embryos which they believe to be the causative agent of primary atypical pneumonia. They found that cotton rats and hamsters inoculated with infected chick embryo materials developed pulmonary lesions and presented evidence to show that patients with the disease develop neutralizing antibodies against this agent. The Commission on Acute Respiratory Diseases, Fort Bragg, N. C.,<sup>3, 21</sup> has reported the transmission of primary atypical pneumonia to human volunteers. Of particular interest is the observation by these workers that approximately 25 per cent of volunteers inoculated with filtrates of sputum and nasopharyngeal washings from patients with primary atypical pneumonia developed the disease. Confirmation of these experimental results which suggest a virus etiology for this form of pneumonia has not yet been reported by other workers.

The isolation from patients with primary atypical pneumonia of a non-hemolytic streptococcus of a single serologic type (streptococcus MG) and the development in such patients of antibodies against two distinct antigenic components of this microorganism have been mentioned. Both the presence of

this streptococcus and the development of antibodies against it in patients have been confirmed by other groups of workers.<sup>5, 18, 19</sup> This microorganism has not been tested for its capacity to produce disease in human beings. Normal persons inoculated intradermally with the capsular polysaccharide of this streptococcus develop in their serum specific antibodies against it, but whether the occurrence of such antibodies in man is accompanied by immunity to the disease is not known.

The present state of information regarding primary atypical pneumonia may be summarized as follows. A closely similar, if not identical, clinical picture may be produced by a variety of different infectious agents known to be pathogenic for man. A very large number of cases has been reported in which these agents of recognized pathogenicity were excluded as etiological factors and in which the causative agent or agents remain uncertain. Whether all of these cases represent infection by the same or different agents is not known. Approximately 50 per cent of patients with primary atypical pneumonia develop in their serum cold hemagglutinins and also agglutinins against streptococcus MG. Although either variety of agglutinin may occur alone, in the majority of instances, when one is demonstrable the other is also, and both are more likely to occur in patients who are more severely ill. These two unrelated reactions provide the best available laboratory procedures in support of clinical diagnosis. Conclusive evidence concerning the infectious agent or agents responsible for the majority of cases of primary atypical pneumonia is still lacking. Present evidence, however, suggests the possibility that both a virus and streptococcus MG may together be implicated in the pathogenesis of this puzzling disease.

## REFERENCES

1. Meyer, K. F.: *Medicine* 21: 175, 1942.
2. Smadel, J. E.: *J. Clin. Investigation* 22: 57, 1943.
3. Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *Bull. New York Acad. Med.* 21: 235, 1945.
4. Curnen, E. C., Mirick, G. S., Ziegler, J. E., Jr., Thomas, L., and Horsfall, F. L., Jr.: *J. Clin. Investigation* 24: 209, 1945.
5. Eaton, M. D.: *Proc. Soc. Exper. Biol. & Med.* 60: 231, 1945.
6. Finland, M., and Dingle, J. H.: *New England J. Med.* 227: 342, 1942.
7. Dingle, J. H., and Finland, M.: *New England J. Med.* 227: 378, 1942.
8. Owen, C. A.: *Arch. Int. Med.* 73: 217, 1944.
9. Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *Am. J. Pub. Health* 34: 347, 1944.
10. Horsfall, F. L., Jr.: *Brennemann's Practice of Pediatrics*, Baltimore, W. F. Prior Co.
11. Schmitz, R. C.: *Arch. Int. Med.* 75: 222, 1945.
12. Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *Am. J. Pub. Health* 34: 335, 1944.
13. Thomas, L., Curnen, E. C., Mirick, G. S., Ziegler, J. E., Jr., and Horsfall, F. L., Jr.: *Proc. Soc. Exper. Biol. & Med.* 52: 121, 1943.
14. Kay, E. B.: *Arch. Int. Med.* 75: 89, 1945.
15. Horsfall, F. L., Jr.: *New York State J. Med.* In press.
16. Thomas, L., Mirick, G. S., Curnen, E. C., Ziegler, J. E., Jr., and Horsfall, F. L., Jr.: *J. Clin. Investigation* 24: 227, 1945.
17. Mirick, G. S., Thomas, L., Curnen, E. C., and Horsfall, F. L., Jr.: *J. Exper. Med.* 80: 391, 407, 431, 1944.
18. Meiklejohn, G., and Hanford, V. L.: *Proc. Soc. Exper. Biol. & Med.* 57: 356, 1944.
19. Finland, M., Samper, B. A., and Barnes, M. W.: *J. Clin. Investigation* 24: 497, 1945.
20. Eaton, M. D., Meiklejohn, G., and van Herick, W.: *J. Exper. Med.* 79: 649, 1944.
21. Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: *J. A. M. A.* 127: 146, 1945.

# DIABETES MELLITUS IN CHILDREN AND THE LEVEL OF CONTROL OF THE DISEASE

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## INTRODUCTION

For many years questions regarding the treatment of young patients with diabetes mellitus as to what constitutes an adequate level of control of the disease. In the present study we have found it practicable to aim to keep the patient away from the toxic reactions and from excreting sugar in the urine while keeping a normal diet.<sup>1,2</sup> As our group has enlarged and the length of observation has lengthened we are endeavoring to evaluate our results to see whether or not anything has been gained by maintaining this high level of control.

The present study was undertaken to determine the relationship between the growth of children with diabetes mellitus and the level of control of their disease.

## SUBJECTS

The records of 134 juvenile diabetic patients under treatment at the Children's Hospital were reviewed for this study. Of these patients 66 are boys, and 68 are girls. The onset of the disease had occurred, for 8 per cent, by the second year; for 52 per cent by the eighth year; and for 92 per cent by the thirteenth year. The median number of years of observation for the 120 children included in the longitudinal study is five years; 10 per cent were observed two years and 13 per cent for ten or more years.

Most of the children are third generation American-born of northern European stock. About one-half of the children are from middle class families with incomes adequate to provide a decent standard of living in the rural communities of Iowa. The remaining one-half are from a low income group who have had assistance from their county, state, and social agencies in order to alleviate a great many social and economic difficulties.

## OBSERVATIONS

At the time of examinations, which were at approximately six-month intervals, a record was made of the child's height and weight. These measurements were plotted on a growth chart and thus was obtained a picture of the child's growth over the years of diabetic care in our clinic. For each child in this study there was a growth chart. There was also available for each patient a summary card that showed, among other items, the level of diabetic control the patient had maintained during the interval between examinations. We have correlated the information available from the growth of the child, and from an over all assessment of the level of control of the disease during the period of treatment.

## METHOD AND PROCEDURE

All of our diabetic outpatients were routinely asked to keep a daily record showing dosage and distribution of insulin; results of examination of three to four urine specimens for sugar; insulin shocks; emotional upsets; infections; and any variation in exercise or diet. The daily records are reviewed at the time of each examination and the level of diabetic control for the period determined and recorded.

The interpretation of the varying levels of diabetic control is given in this tabulation:

- Very good-to-excellent:* Urine specimens are free from sugar except for very occasional traces; very occasional mild insulin shocks
- Good:* Urine specimens free from sugar except for occasional traces; occasional mild insulin shocks
- Fair-to-good:* More than one-half of the urine specimens free from sugar but minimal glycosuria in remaining specimens; occasional insulin shocks of varying degree
- Fair:* Less than one-half of the urine specimens free from sugar and varying amounts of sugar in remaining specimens; occasional insulin shocks of varying degree
- Poor:* Urine specimens contain varying amounts of sugar continuously; occasional insulin shocks

For the majority of the children there were no wide fluctuations in the level of control over several years. Many fluctuated from one level to an adjoining one. For these we gave the classification of the level that prevailed for the most part. This scale graded the 120 children into groups ranging from poor to excellent diabetic control during the period of growth.

To evaluate the growth of the juvenile patients the height and the weight were observed at each examination. These values were plotted on a growth chart for the individual. Thus his progress was charted and a valuable pictorial record of his growth was obtained. (Figs. 1 and 2.)

Several authors studying the growth of diabetic children have questioned whether or not the available norms were suitable to evaluate the growth of their particular groups. We consider this an important issue. For this study the Iowa City Growth Charts were used.<sup>3</sup> These charts were devised using Iowa City data because it is believed they give a standard of growth that approaches the optimum for general pediatric practice. This high level accrues from the selection of subjects, most of whom were favored by environment.

The background of the children in the present study is similar to the children on whom the growth charts are based, geographically and as to the time the observations were made; and to a large extent both groups are American born of northern European origin. The socioeconomic level of the study group is lower than that of our norms. Provision for nutrition of many of the diabetic patients was substandard before admission to our clinic. The regimen of therapy for the diabetic child in our clinic provides for excellent nutrition and since the diabetics are supervised more closely than nondiabetics



it is likely that their regimen was superior to that followed in general by the children on whom the norms are based.

The growth curves of the patients used in this study extend over at least a two-year period and the average length of observation is five years. In order to have more nearly homogeneous groups we considered separately the growth before 10 years of age and the growth after 10 years. In the years before 10 there are fifty-four subjects and in the years after 10, ninety-three subjects.

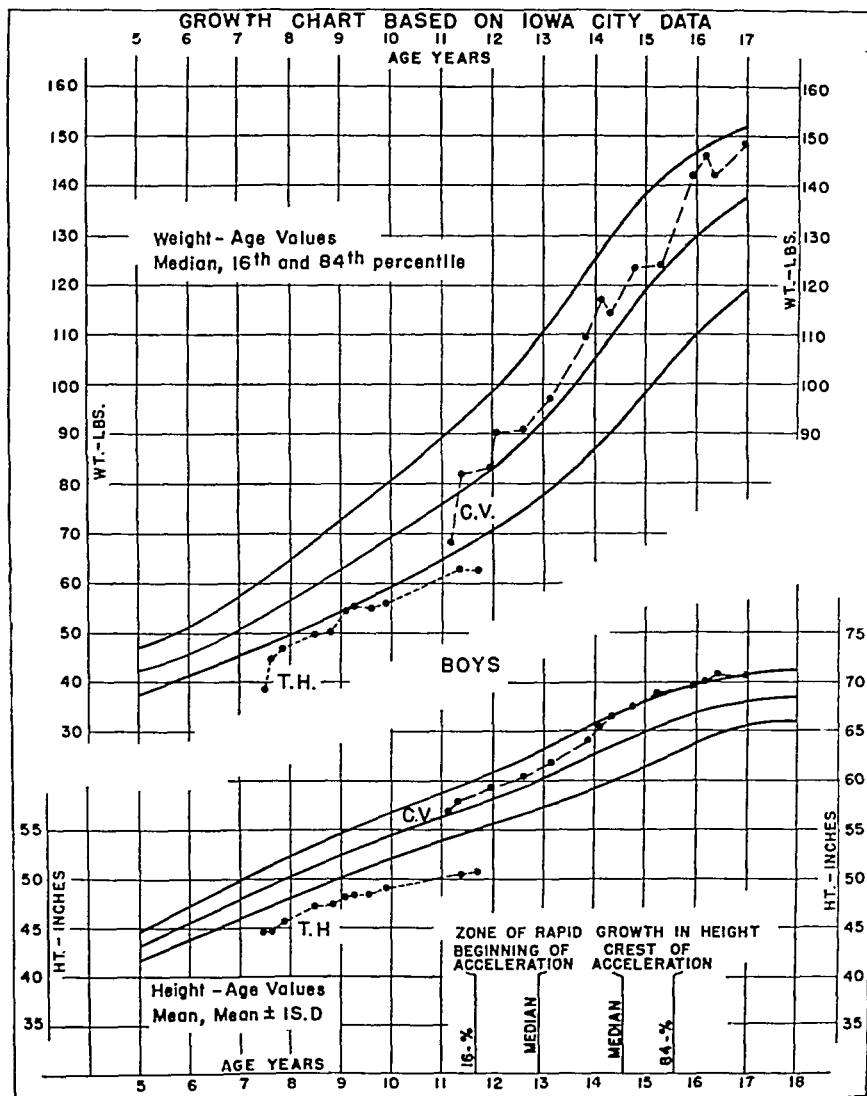


Fig. 1.—The growth curve of C. V. was selected to demonstrate the satisfactory growth in height and weight of a boy with moderately severe diabetes kept under excellent control. The growth chart of T. H. illustrates the unsatisfactory growth in height of a child with moderately severe disease kept under poor diabetic control.

In studying these growth charts with the view to correlating the growth evaluation with the level of diabetic control we have designated the rate of growth:

*Accelerated:* The curve of the individual's height follows a course that is more steeply inclined than the curve of the chart for the whole period of observation or for part with the remaining part normal growth

*Normal:* The curve of the individual's height parallels the curve of the chart

*Less:* The curve of the individual's height follows a course less steeply inclined than the curve of the chart for the whole period of observation or for part with the remaining part normal

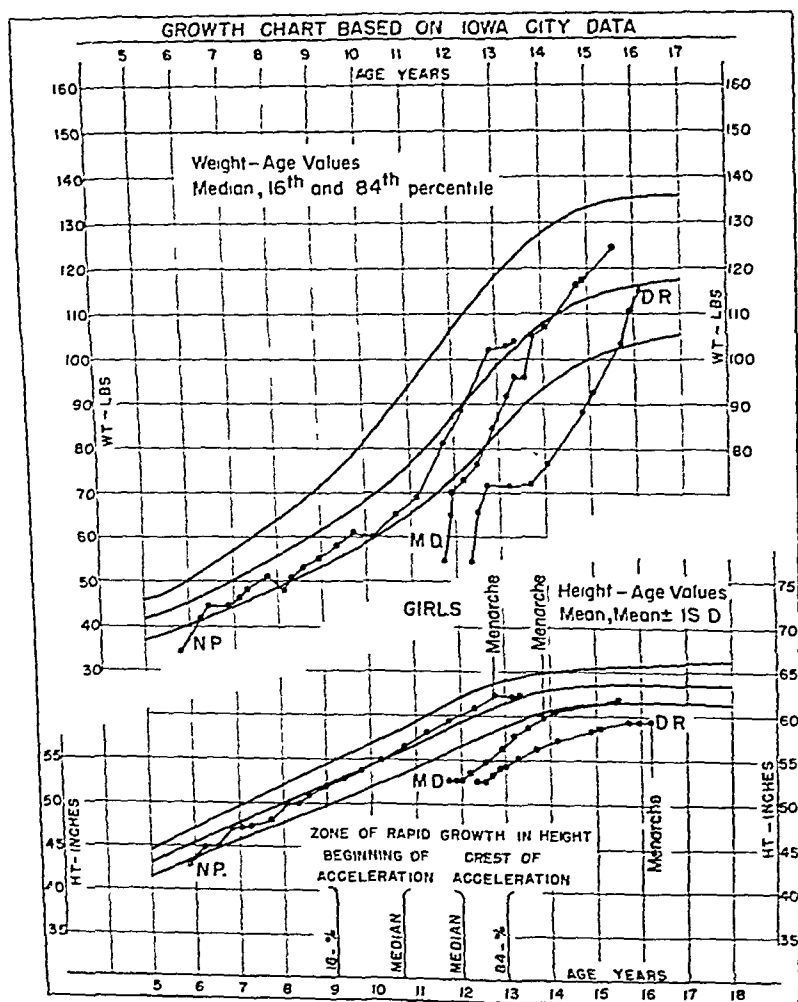


Fig. 2—N. P.'s growth chart was selected to demonstrate the growth of a child with early onset of diabetes. Her disease was severe but kept under excellent control throughout childhood. She had accelerated height gains and matured normally. M. D. and D. R. are clinic about one year after onset. At the time of first examination both were more than 2 standard deviations below the average height for their age. M. D.'s disease was under good control and D. R.'s control was poor. M. D. made better height gains and matured more normally than D. R.

*Erratic:* The curve of the individual's height changes its course from a period of accelerated to a period of less than normal growth or vice versa

#### FINDINGS

*Height at Beginning of Treatment.*—The children came to our clinic at varying lengths of time after the onset of the disease, and so we have height and weight observations on only a small proportion at onset. Eighty-six of the patients were admitted within six months of the onset of diabetes. It is conceded that within six months the disease could have had its effect on height. Nevertheless we are considering any height observation made within six months of onset as proportionate to his height at onset and comparing the heights of the group with the norms, to see if our group of diabetics at the onset of the disease deviated significantly in height from the Iowa City norms. The heights of 36 (42 per cent) children deviated less than  $\pm 1$  standard deviation from the average height for age as given by the norms. Thirty-five (41 per cent) of the children were 1 standard deviation or more below the average. Fifteen (17 per cent) were 1 standard deviation or more above the average height for age. Judging the diabetic sample of height at onset by the sample of Iowa City children on which the Iowa City Growth Charts are based, there were fewer heights in the zone average  $\pm 1$  standard deviation than expected, and more than the expected number were 1 standard deviation or more below the average. This might be interpreted as indicating the standards are high for the group of children on a socioeconomic basis. However, since many children showed accelerated growth after the diabetic regimen at our clinic was begun, we are inclined to interpret the greater number of shorter children as a failure to grow properly under their former regimen. The distributions of height deviation from the norm at onset and at last observation of 86 patients are:

HEIGHT DEVIATION (STANDARD DEVIATION UNITS)	OBSERVATION WITHIN SIX MONTHS OF ONSET	LAST OBSERVATION
-2 and under	6	7
-1 to -1.9	29	16
-.9 to +.9	36	47
+1 to 1.9	12	14
2 and over	3	2

At the beginning of treatment at our clinic 22 patients' heights deviated from the average a negative 2 standard deviations or more. Twelve of these patients were seen within two years of the onset of the disease. The five children with the most stunting (negative 3 standard deviations or more) were admitted to our clinic two to seven years after the onset of the disease.

Later, of these 22 patients,

- 13 had accelerated growth rates
- 5 had normal growth rates
- 2 had erratic growth rates
- 2 had less than normal growth rates

*Growth in Height in Relation to Level of Control.*—Fifty-four patients comprise the group with early onset of diabetes and with records for at least two years prior to 10 years of age. This group was observed during the part of the growing period which is characterized, in general, by relatively slow and regular linear growth. A second group of 93 children was observed after they had reached their tenth year and during the ages when children, in general, have a "spurt" of growth. On the whole, the rate of growth of these older children is difficult to evaluate since there are a number of factors that make growth at this age unpredictable for even the well child.

TABLE I

LEVEL OF CONTROL OF DIABETES MELLITUS	GROWTH IN HEIGHT BEFORE 10 YEARS OF AGE COMPARED WITH THAT OF AVERAGE IOWA CITY CHILDREN <sup>3</sup>									
	LESS		ERRATIC		NORMAL		ACCELER- ATED		TOTAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Poor	3	38	1	12	3	38	1*	12	8	
Fair	3	25	1	8	8	67			12	
Fair-to-good			3	19	10	62	3	19	16	
Good	1†	8	1†	8	3	25	7	58	12	
Very good-to-excellent					2	33	4	67	6	
Total	7	13	6	11	26	48	15	28	54	

\*This patient accelerated the first year of treatment when he was under fair-to-good diabetic control. He was emaciated at the time treatment was started and had been under poor diabetic control for more than one year.

†These patients failed to keep their appointments at the clinic, and their diets were not increased to satisfy their appetites.

*Group Observed Before 10 Years of Age.*—In the younger age group 20 of the 54 children were under poor or fair control (Table I). Of these 20 only one patient accelerated in growth and that was during his first year of treatment when he was kept under fair-to-good diabetic control. Of the seven children who grew less in height than expected, six were in poor or fair diabetic control, and one was in good diabetic control but his history reveals that he failed to keep his clinic appointments and his parents did not increase his diet properly from age 5 to 8 years. Fifteen of the 54 children (28 per cent) made accelerated growth and all of these patients were under fair-to-good, good, or very good-to-excellent diabetic control, except the one child in poor diabetic control who has been discussed. From these findings it is apparent that children under poor diabetic control have a great likelihood of growing less in height than expected, that children under fair or fair-to-good diabetic control have a good chance of growing at an average rate, and that children under good or very good-to-excellent diabetic control have the opportunity of making compensatory or accelerated growth. The data of Table I, analyzed statistically, give chi-square equals 27.69 which is significant beyond the 1 per cent level of confidence.

*Group Observed After Ten Years of Age.*—Of the 93 diabetic children for whom we have growth charts and observations after 10 years of age a group of

34 had the onset of the disease before 9 years of age and received treatment in our clinic before 9 years; a second group of 11 patients had the onset before 9 years of age and received treatment at our clinic after 9 years of age; and a third group of 38 had the onset of the disease after nine years of age and received treatment in our clinic while they were still in the growing period (Table II).

TABLE II. GROWTH IN HEIGHT OF DIABETIC CHILDREN AFTER 10 YEARS OF AGE COMPARED WITH THAT OF AVERAGE IOWA CITY CHILDREN

LEVEL OF CONTROL OF DIABETES MELLITUS	LESS	ERRATIC	NORMAL	ACCELERATED	EXTENDED GROWING PERIOD (GIRLS)	TOTAL
<i>Group I</i>	<i>Onset before 9 years and hospital treatment before 9 years</i>					
Poor	2		2			4
Fair	2		7	1		10
Fair-to-good	1		6	6		13
Good			2	3		5
Very good-to-excellent			1	1		2
<i>Group II</i>	<i>Onset before 9 years and hospital treatment begun after 9 years</i>					
Poor						
Fair	1			4	1 of 6	6
Fair-to-good			3	2	0 of 4	5
Good						
Very good-to-excellent						
<i>Group III</i>	<i>Onset after 9 years and hospital treatment after 9 years</i>					
Poor					1 of 1	1
Fair			6		1 of 3	7
Fair-to-good		1	4	12	1 of 5	18
Good	1†		7	4	3 of 9	15
Very good-to-excellent			4	2	1 of 4	7
Total	7	1	42	35	8	93

\*Although this overprotected boy had rather frequent and marked glycosuria it was primarily caused by diet indiscretions. The glycosuria was always of short duration as larger doses of insulin were given by the mother.

†This patient, a boy, was admitted for treatment at our clinic when 14 years, 5 months old. This was ten months after the onset of the disease. His height previous to admission is not known. He made normal gains up to 16 years, after which he grew less than expected. It is difficult to say whether or not his growth was arrested too early, but from 16 to 20 years he grew only one-half inch. His height at last observation was 67.1 inches.

Group I represents a wider range of diabetic control than the other two groups observed after 10 years of age. Unfortunately, from the point of view of our study, there is no patient with poor control in Group II and only one in Group III. There are also several cases in which the children seem to be having prepuberal growth disturbances in height but these cannot be properly evaluated until they have been observed a few more years.

The distribution of cases of Group I according to level of diabetic control and growth in height shows that there is a likelihood for children under poor control to grow less than expected. With fair control children have a good chance to make average height gains and with a fair-to-good or better level of control many may show accelerated growth. D. B., a girl in Group I, exemplifies one of the difficulties encountered in evaluating the growth of children in this age period. She was under fair-to-good control and grew less than expected from 10 to 13½ years. She is being observed currently. Menarche has not occurred and there is the possibility that she may have late menarche

and an extended growing period. At 13½ years her height is 53.6 inches which is about 4 standard deviations below the mean for her age.

The distribution of cases of Group II according to level of diabetic control and growth in height shows that children who have had the disease poorly controlled for two or more years and then are placed under our regimen of therapy frequently show accelerated growth rates with only fair control. That all the children in this group were maintained on fair or fair-to-good diabetic control also confirms our clinical experience that it is difficult to maintain children on good or excellent control after years of poor diabetic management. B. S., a girl, is the only patient in Group II who grew less than expected during observation. The onset of her disease was at 8 years and she was admitted to the hospital clinic two years later. Under a fair level of control she grew less than expected from 10 to 16 years. Menarche had not occurred at 16 years. At 10 years her height was a negative 1½ standard deviations and at 16 years a negative 2¼ standard deviations from the mean for her age.

We have noted for a number of girls that the growing period has been extended a few years beyond that which is usual for girls in general. (Table II.) The data are not sufficient to permit any conclusions as to the relation of this type of growth to level of control. The factor of sex assumes more importance in evaluating the growth disturbances in this older group of children than it does in the group observed before ten years of age.

In Group III only one child is rated as under poor control. The growth of this girl, D. R., is shown in Fig. 2. Her menarche occurred at 16 years, 2 months, and her growing period was longer than usual. There apparently was a growth disturbance. On the chart her growth is contrasted with that of M. D., a girl, who was under good control. M. D. had her acceleration in growth between 12 and 14 years and menarche occurred at 13 years, 9 months. There were no obvious failures to grow in this group.

For this group of children (not including the seven girls with extended growing period) who had the onset and hospital treatment after 9 years of age, those under fair control made average gains and those under fair-to-good, good, or very good-to-excellent diabetic control made average or accelerated gains.

*Erratic Height Gains and Level of Control.*—On evaluating the growth of the children for the whole period of observation we found six children with erratic growth. Three of the children who had definite and prolonged periods in various levels of control showed a positive correlation between level of diabetic control and growth in height. During periods of lower levels of control the growth in height was less than expected and during the periods of higher levels of control the growth in height was normal or accelerated. For the other three children who had changes in level of control not so pronounced or prolonged the correlation with growth, if any, was indeterminate from our observations. However, these three children did have erratic levels of diabetic control as well as erratic height gains.

*Menarche of Diabetic Girls in Relation to Level of Control.*—Menarcheal histories are available for 35 of 46 diabetic girls observed during the years of expected menarche. Seven girls had their first menstrual period before the onset of diabetes—two at as early as 11 years. Twelve of the 28 girls remaining had the onset of the disease before 9 years. The three girls who were under very good-to-excellent diabetic control matured normally. Of the five girls who were under fair-to-good diabetic control, three matured normally and two were delayed. All of the four girls who were under fair diabetic control were delayed in maturing.

Sixteen of the 28 girls had the onset of diabetes between the years 10 and 14. Nine of these were under good-to-excellent diabetic control. Six of these matured normally and three were delayed. J. E., of this group, was 14 years and 10 months old on admission to this clinic, which was three years after the onset of the disease. Menarche occurred at 17 years. R. N., another of this group, had her disease one year before admission to our clinic at the age of 12 years, 10 months. Menarche was at 15 years, 10 months. M. L. A., also of this group, was 13 years and 8 months old at the time of the onset of her disease. She was admitted to the hospital three months after onset and her menarche occurred at 16 years, 8 months. Of the three who were in fair-to-good diabetic control two matured normally and one was delayed. Of the four who were in fair or poor diabetic control, one matured normally and three were late. A longer than average growing period was generally coexistent with delayed menarche. This relationship was present for 11 of 13 patients.

*Growth in Weight Observed for the Total Group.*—With adequate management the diabetic children, on the whole, have maintained normal weight for their age and height, and have gained normally during the years of observation included in this study. Twenty-six children were observed to have a tendency to become obese. Some of our well-regulated diabetics made no gains or had losses in the summertime when exercising more than usual.

The trend toward obesity was observed in 21 of the 26 children during the ages 14 to 18 years. For the remaining five children the tendency to obesity occurred during the earlier years of childhood. The overweight for height and age was corrected for three of the children by improving their regimen. The two other children were observed seven and nine years; one was under fair-to-good diabetic control, the other under poor diabetic control; both grew less in height than expected and remained overweight for their age and height.

The children who were underweight at the time of admission to our clinic responded readily to treatment and were back to normal weight for age and height in about six weeks.

A larger proportion of the girls (approximately 34 per cent) than boys (approximately 17 per cent) of those observed at the ages from 14 to 18 years showed accelerated weight gains and drifted toward obesity. Following is a tabulation of the children who showed a drift toward obesity in relation to the level of control of their diabetes.

LEVEL OF CONTROL OF DIABETES	NUMBER OF	NUMBER OF
	BOYS	GIRLS
Poor	1	3
Fair	2	8
Fair-to good	2	4
Good	0	1
Very good-to excellent	0	0
	—	—
Total	5	16

Sixty-seven per cent of those who had accelerated weight gains with a tendency to become obese were in poor or fair diabetic control. Girls often manifested this tendency to become obese after menarche had been established.

*Severity of Disease.*—Using the common index of the severity of the disease, the amount of insulin required per kilogram of body weight, we found there was a tendency for those with less severe disease to be under the best control. However, there is a representative number of patients with moderately severe and very severe diabetes under each of the designated levels of control. Of 95 patients with moderately severe or very severe diabetes:

- 8 are under very good-to-excellent diabetic control
- 15 are under good diabetic control
- 37 are under fair-to-good diabetic control
- 26 are under fair diabetic control
- 8 are under poor diabetic control

*Growth of Children With Severe Diabetes and Level of Diabetic Control.*—Of the eight patients with moderately severe or very severe diabetes under very good-to-excellent diabetic control, four accelerated and four grew normally. All of these children were adequately treated shortly after the onset of their disease. None of these children were below expected height for their age at the time of their initial examination.

A group of ten children, who had moderately severe or very severe diabetes and an early onset of the disease so that they were observed at least two years before the age of 10 years, were under good, very good, or excellent diabetic control. Seven of these children had accelerated growth in height, two made average gains, and one grew less than expected. It is known definitely that the last child, during a lapse of three years from the clinic, did not increase his diet to satisfy his appetite. This small but homogeneous group supplies evidence that children with severe disease grow well if adequately managed.

A similar group of seven children with moderately severe or very severe diabetes with early onset and under prolonged poor control included three who made average gains, one who was erratic, and three who grew less than expected.

#### DISCUSSION

Numerous growth studies of children with diabetes mellitus have been reported.<sup>4-21</sup> These studies reveal that compensated diabetes is compatible with



The growth of children after 10 years is more unpredictable and difficult to evaluate than the growth before 10 years. The differences in growth of the children observed after 10 years of age grouped according to level of diabetic control show a consistent tendency to be normal or accelerated for the better levels of control and to be normal or less than expected for fair or poor diabetic control. In this group are eleven children who were admitted to our clinic two to nine years after onset of the disease and during the intervening time they had been in poor diabetic control. Four of these patients accelerated after coming under our regimen of therapy even under fair diabetic control.

There is a tendency for the girls in the higher levels of diabetic control to mature normally and for those in the lower levels of diabetic control to be delayed in maturing. A longer than average growing period is generally coexistent with delayed menarche. When the onset of diabetes occurs during the years 10 to 14, it is likely to interfere with the maturation processes. Three of nine girls who were under good-to-excellent diabetic control had delayed menarche; three of four girls under fair or poor diabetic control had delayed menarche. There is confirming evidence in this study that girls with the onset of the disease before 9 years mature normally when kept under good or excellent diabetic control.

Severity of the disease is related to the level of control in that the children with the less severe disease tended to maintain the higher levels of control and all in the poor control group had moderately severe or very severe disease. Growth was evaluated in a group of ten children with early onset of diabetes in whom the disease was moderately severe or very severe and kept under good or excellent control. This group of children showed above average propensities to grow during the period of observation. Severity undoubtedly adds to the problems of control but does not appear to be the determining factor in regard to growth when the disease is well controlled.

This study demonstrates the importance of early and complete management in order to prevent retardation of growth and development. For the children already stunted from improper care the importance of complete management is also demonstrated as a means of ameliorating retardation of growth and development.

#### REFERENCES

1. Jackson, R. L., Boyd, J. D., and Smith, T. E.: *Am. J. Dis. Child.* 59: 332, 1940.
2. Jackson, R. L., and McIntosh, C. B.: *Am. J. Dis. Child.* 70: 307, 1945.
3. Jackson, R. L., and Kelly, H. G.: *J. PEDIAT.* 27: 215, 1945.
4. Joslin, E. P., Root, H. F., and White, P.: *J. A. M. A.* 85: 420, 1925.
5. Ladd, W. S.: *Am. J. Dis. Child.* 32: 812, 1926.
6. Boyd, J. D., and Nelson, M. V.: *Am. J. Dis. Child.* 35: 753, 1928.
7. Boyd, J. D., and Kantrow, A. H.: *Am. J. Dis. Child.* 55: 460, 1938.
8. McGavin, A. P., Schultz, E., Peden, G. W., and Bowen, B. D.: *New England J. Med.* 223: 119, 1940.
9. Wagner, R., White, P., and Bogan, I. K.: *Am. J. Dis. Child.* 68: 667, 1942.
10. Fischer, A. E., Mackler, H. S., and Marks, H. H.: *Am. J. Dis. Child.* 64: 413, 1942.
11. Barach, J. H.: *Proc. Am. Diabetes A.* (1944) 4: 169, 1945.
12. Nelson, W. E., and Ward, D.: *Am. J. Dis. Child.* 55: 487, 1938.
13. Jackson, R. L., and Kenefick, J.: *Am. J. Dis. Child.* 64: 807, 1940.

# THE HYPOXIA TOLERANCE TEST OF THE HEART IN CHILDREN\*

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MODERN cardiological examination methods have gradually improved the possibilities of definite diagnosis, thereby adding to the prerequisites of appropriate treatment. In this way, more reliable information regarding the function of the heart during normal as well as pathologic conditions has been obtained. When, as is often the case, special heart function tests are described, it is easy to forget that all the common symptoms of a cardiac disease frequently form simultaneous indications of an unstable cardiac function. Dyspnea, nycturia, albuminuria, prolonged P-Q time in the electrocardiogram, and gallop rhythm in the phonocardiogram, to take a few examples, may all be signs of deteriorated cardiac function. This notwithstanding, it has long been realized that our knowledge of the relative heart insufficiency is inadequate. Much would be gained, could the heart be subjected to a tolerance test through an extra amount of exertion so as to produce, in a subject with latent decompensation, a reaction which would not occur in the case of a healthy person. Modern tolerance tests in adults have been worked out on the basis of this reasoning. The patients have been given various drugs, such as digitalis, and the cardiac effect has then been observed by means of electrocardiographic registration. Individuals with healthy hearts and those with diseased hearts have been made to do exercise of various kinds, as for instance, measurable work on a bicycle, or walking up and down a specially constructed flight of stairs at a known pace. Afterward the heart's response to the tolerance test has been registered in different ways (Nylin, Klemola). The drawback of such a procedure is that the effect is recorded *after* the termination of the exertion, in which case it should be noted that the heart undergoes an exceedingly rapid change after the completed tolerance test (Liljestrand and associates). Furthermore, these tests are unsuitable in the examination of children, however instructive they may be when adapted to adult patients.

In 1933 Dietrich and Schweigk for the first time made use of exhaled air with a reduced oxygen content for the purpose of studying the effect on the heart. This method has later been adopted by several investigators, of which Larsen (1938), Levy and associates (1940), Åkesson and Malmström (1945), Björck (1945), and Pruitt and associates (1945), may be mentioned here. All of them dealt with adult patients. The principal aim of their investigations has been to analyse the conditions of coronary insufficiency. Larsen had, in addition, observed the effect of hypoxia on patients suffering from diabetes, myxedema, as well as in a few cases of valvular diseases and myocarditis. Furthermore, tests of this kind have been employed in aviation-medicine investigations. I have not been able to find any data regarding such tolerance tests on children.

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normal growth but that many children with the disease do not grow normally. The importance of an adequate diet has been established for the diabetic as well as the nondiabetic child.<sup>12, 13</sup> The hereditary, geographic, and socioeconomic factors can be minimized in evaluating the growth of a child by using a method which studies the child not only as he grows in relationship to others, but as he establishes and maintains his own pattern of growth. A factor which has not been given sufficient emphasis in most of the studies is the importance of the level of control of the disease.

Ladd<sup>5</sup> observed that a diabetic child will grow well when he is kept sugar-free and receiving an adequate diet. Boyd and Nelson<sup>6</sup> state that "the child will grow normally providing the control is such that prolonged or repeated hyperglycemia is avoided and the child's nutritional requirements met by an adequate diet." Boyd and Kantrow,<sup>7</sup> studying the retarded group of children in this clinic prior to 1935, demonstrated that many of the children receiving an adequate diet and on a high level of diabetic control showed acceleration of growth. Wagner, White, and Bogan<sup>9</sup> found no relationship between retardation of growth and level of control of the disease. These authors consider a child in very good diabetic control if he is excreting no more than 10 per cent of the ingested carbohydrate, in good diabetic control if he is excreting no more than 20 per cent of the ingested carbohydrate, and in poor diabetic control if he is excreting more than 20 per cent of the ingested carbohydrate. We are of the opinion that any child excreting as much as 10 per cent of his ingested carbohydrate is approximating poor diabetic control. The very good control group, as defined by these authors, would include the first four groups by our standards of control (very good-to-excellent, good, fair-to-good, and fair). The good control group by their standards would comprise, for the most part, our poor control group.

The differences in the findings on the status of the height of the child at onset of diabetes by several authors may, in a large measure, be accounted for by the differences in the appropriateness of the standards used in evaluating the groups and by a difference in the opinion of the several authors as to what constitutes a tall or short child. Fischer and associates<sup>10</sup> found a tendency to be tall for the children whom they studied. We have found more than the expected number of children to be short. Whereas they considered a child tall if he were one inch or more above the mean of the Burgess standard of height for his age, using the Iowa City Growth Charts we considered any child tall who was 1 standard deviation or more above the mean height for that age. The standard deviation increases with age from approximately one and one-half inches at 5 years to three inches at 12 years.

Recognizing that the nutritional advice was followed more carefully by some patients than by others and that errors in diet were a major factor many times in causing glycosuria, it is our belief that the children generally were offered an excellent diet. Some of the children in poor diabetic control neglected to carry out instructions including dietary advice, and therefore some of their retardation of growth may have been on a dietary basis. Some of the children who grew less than expected and were under poor diabetic

control were known to be receiving an adequate diet. The younger group of children under fair diabetic control and known to be receiving an adequate diet occasionally grew somewhat less than expected and at best made normal increments of growth. Acceleration occurred in the younger group of children only when they were receiving an adequate diet and maintained a good level of diabetic control. In the older group of children four patients under only fair diabetic control had accelerated growth. All of these children had been treated elsewhere for at least two years under poor diabetic control and with a questionably adequate diet. The majority of recent studies reported in the literature consisted of children receiving adequate diets but under less rigid levels of control. These children have not grown as well as those observed by us receiving comparable diets but who maintained a higher level of diabetic control.

Avoidance of retardation both of growth and of maturation is important from the psychological as well as the physical basis. McGavin and associates<sup>5</sup> found that many children were more disturbed emotionally over their short stature than by the fact that they had diabetes. The children had a tendency to become seclusive or compensated by a show-off behavior and boastfulness, exaggerating everything they said or did.

No child observed in this group had clinical evidences of endocrine disturbances other than hypoinsulinism.

#### SUMMARY AND CONCLUSIONS

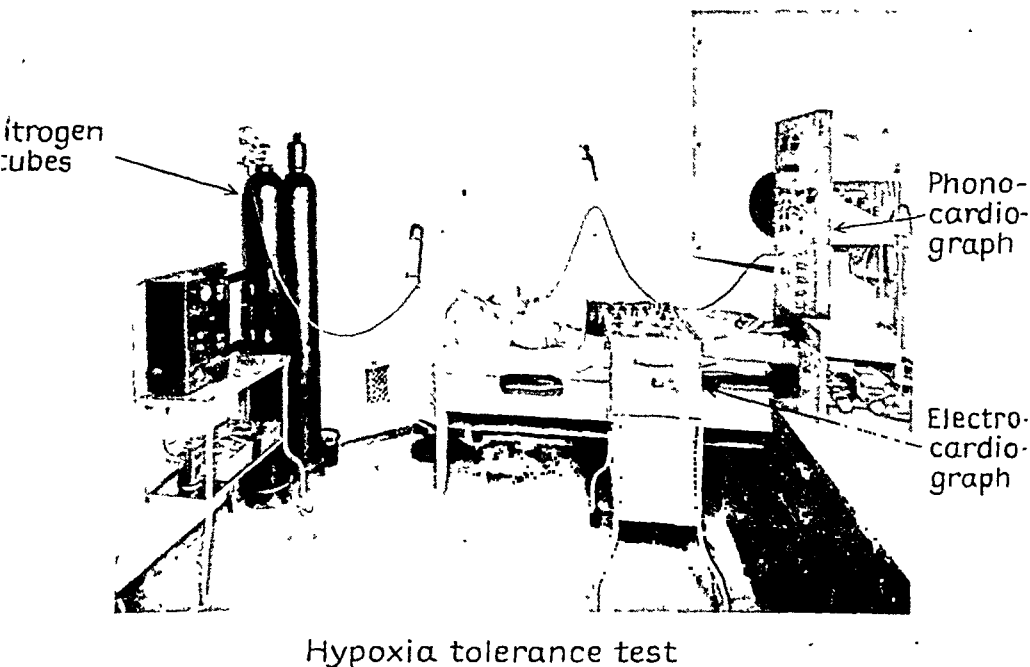
The growth of the 120 diabetic children in this study group showed a much stronger tendency to be normal or to be accelerated than to be retarded.

In evaluating the growth of the diabetic children the Iowa City Growth Charts were used. These standards are comparatively high, but the background of the children in the study group is similar in many ways to that of the children on whom the standards are based.

For the study of the relation of growth in height to level of diabetic control the data have been broken down into groups, one of which consists of observations before 10 years of age and the others of observations after 10 years of age. This was done to segregate the characteristics of growth associated with prepuberty.

The differences in growth of children grouped according to the level of control of diabetes are significant for those observed before 10 years. Table I shows that children under good-to-excellent diabetic control have a better chance to accelerate than those under lower levels of diabetic control. Those under poor diabetic control or fair diabetic control did not accelerate. Six of the seven children who grew less than expected were classified as being under either poor diabetic control or fair diabetic control. Normal growth was found for approximately two-thirds of those under fair or fair-to-good diabetic control, but since many of these children have some retardation we feel that compensatory growth might have been effected by a better level of control of the disease. Erratic growth is more frequent for children in fluctuating levels of control.

Since 1937, when I had the opportunity of studying this method with Larsen at the Warburg Clinic in Copenhagen, I have had the idea of applying this method to a representative group of children. The greatest obstacle which had to be overcome was of a purely technical nature. It concerned the apparatus. Without access to an under-pressure chamber, and also considering the fact that children cannot without difficulty be made to breathe through a mouthpiece or into a "rebreathing apparatus," my first task was, of course, to construct a new apparatus which would be suitable for children of all ages. Quite a number of models have since appeared, each showing further simplification.



Hypoxia tolerance test

Fig. 1.

The apparatus now in use seems to function quite satisfactorily and has been constructed in collaboration with Mr. Emil Andersson, civil engineer at The Swedish Gasaccumulator Company in Stockholm. In principle, it represents a further development of the oxygen-carbon-dioxide mixer employed for oxygen therapy, which was described in 1939, by Lichtenstein and Mannheim.

The apparatus functions thus: The nitrogen contained in a cylinder is conducted to an injector recording a certain volume per time unit. In our investigation, we chose the quantity of 7.8 liters of nitrogen per minute. The injector is constructed to suck in a certain amount of air simultaneously with the nitrogen. The air is made to pass through a rotameter with a float, which can be maneuvered into any desired position, denoting the quantity of air per minute. The respiration chamber is delimited by an adjustable metal ring with

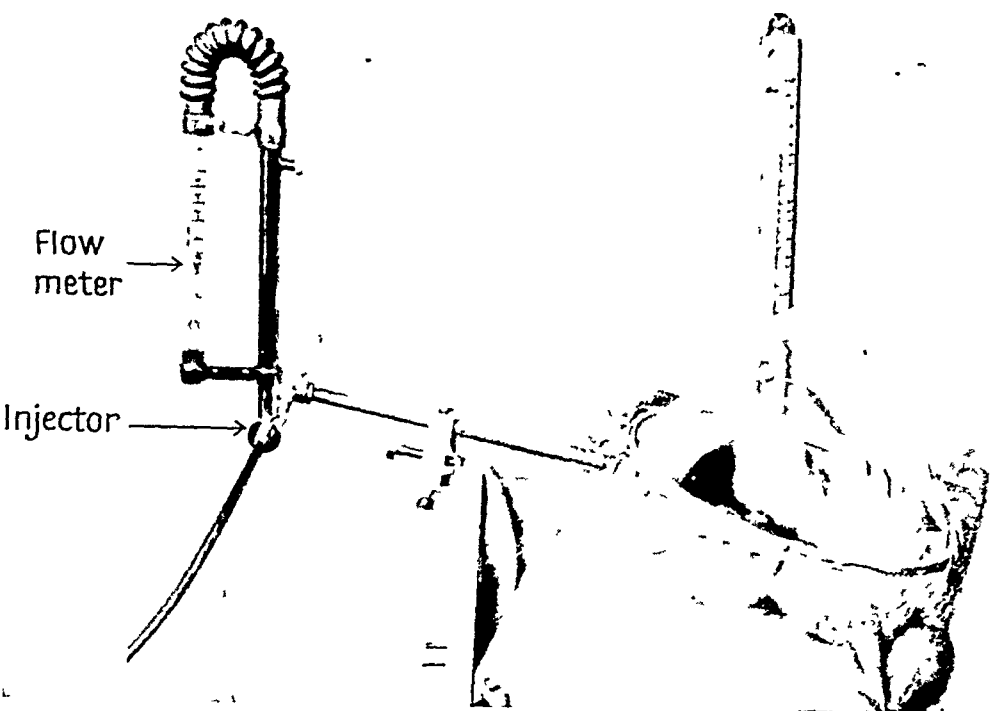


Fig 2

NORMAL CASE 97

Girl, 10 years

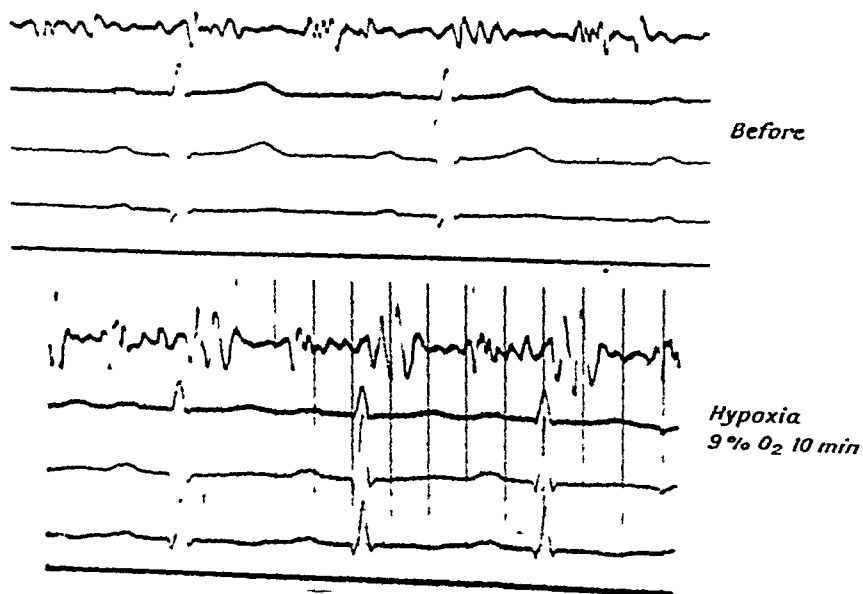


Fig 3

an attached oiled silk covering, onto which a hood of Plexiglas is placed. The increased ventilation (approximately 15 liters of gas per minute) causes such strong over-pressure as to render unnecessary special precautions to keep the oiled silk perfectly close to the back, shoulders, and chest of the subject. The hood of Plexiglas may be lifted off the metal ring at any time, if the patient should become restless or feel ill. A pipe from a cylinder of carbogen should be introduced into the respiration chamber to be at hand in case of danger. By varying the amount of inhaled air, a suitable oxygen content is obtained in the respiration air, from 6.8 to 11.7 per cent (Figs. 1 and 2). Table I gives one of the numerous attempts to determine the oxygen content in the respiration air. It will be seen that constant conditions prevail after four and one-half minutes. The uniform results obtained from recent control tests have afforded complete confidence in the contention that the oxygen content in the respiration air is in accordance with the value disclosed by the position of the rotameter (Table I).

TABLE I. OXYGEN DETERMINATION IN RESPIRATION AIR

Nitrogen 7.8 liters per minute	
Oxygen 6.4 liters per minute	
Theoretical result $\frac{x}{100} (7.8 + 6.4) = \frac{20}{100} 6.4$	
$x = 9\% O_2$	
MINUTES	OXYGEN %
3	10
3½	9.6
4	9.5
4½	9.1
11	8.7
16	8.8

As a rule, the test has been carried out with 9 per cent oxygen for ten minutes. After this time, the patient remained lying down for five minutes. The electrocardiogram and the phonocardiogram registered before the test, and five, ten, and fifteen minutes after. The pulse was counted every other minute.

The results presented are of a preliminary nature. The normal data as well as the data from different cardiac diseases are not as yet comprehensive enough to warrant a statistical analysis, nor to make possible an exhaustive answer to the question of the value of this test. When, nevertheless, I have ventured to submit the results hitherto achieved, the reason is simply that the outcome thus far has been so encouraging as to justify a reference even at this moment to a tolerance test which should serve its purpose well in routine clinical work. The test takes only fifteen minutes and is easy to perform and, according to present experience, free from risks. In addition, the fact that all of the electrocardiographic changes and the rate of the pulse, five minutes after the termination of the treatment have resumed their original state before the test shows that the test can be adopted without risks (Figs. 5 and 7).

Several different criteria have been suggested with regard to positive hypoxia tests (Levy, Larsen, and Åkesson and Malmström). In the estimation of the values obtained I have not followed in detail any of the procedures

hitherto proposed. Instead, I have regarded the normal cases as a physiologic unit, considering definite deviations from it as pathologic. This has been feasible since the normal cases showed, without exception, insignificant changes during the tolerance test. Without doubt, the pediatrician is, in this respect, in a far more favorable position than specialists in internal medicine. It is no easy matter to procure normal data from, shall we say, patients from 40 to 50 years old with intact myocardium. Circumstances are quite different in regard to children's hearts which are normally healthy and strong (Fig. 3). This has formed the basis of the following criteria of positive hypoxia.

1. Electrocardiogram: A depression of the S-T intervals in Leads I or II of at least 1 mm.
2. Electrocardiogram: Negative or diphasic T<sub>1</sub> or T<sub>2</sub>.
3. Electrocardiogram: Marked changes in the P-Q time.
4. Phonocardiogram: Appearance of gallop rhythm.

The age distribution of the cases is illustrated in Table II. Table III shows the pathologic cases hitherto examined, as well as the results obtained, in hypoxia tolerance tests.

TABLE II. CASES DISTRIBUTED TO AGE AND SEX

AGE (YR.)	NORMAL CASES		PATHOLOGIC CASES	
	BOYS	GIRLS	BOYS	GIRLS
1 to 5	1	1	3	4
6 to 8	3	5	8	6
9 to 11	4	8	4	7
12 to 14	2	1	4	11
15 to 17	4	1	3	4
Totals	14	16	22	32

TABLE III

	NUMBER OF CASES	HYPOXIA 9% O <sub>2</sub> 10 MIN. RESULT	
		POSITIVE	NEGATIVE
Normal cases	30	0	30
Rheumatic carditis { active	7	7	0
{ healed	1	0	1
Patent ductus Botalli	6	5	1
Congenital defect without cyanosis	5	1	4
Congenital defect with cyanosis (morbus ceruleus)	1	1	0
Chronic polyarthritis	1	1	0
Myocardial failure	4	3	1
Gallop rhythms	29	9	20

All the normal cases have disclosed negative results in the tolerance test. Seven cases of active rheumatic carditis have all been positive (Figs. 6, 7, and 8). Not less than three of these cases lacked definite electrocardiographic indications of the rheumatic infection. One case of a healed rheumatic carditis, without the slightest sign of a decompensated heart, had negative results.

Six cases of patent ductus Botalli have been examined. Not less than five of them were positive. However, this does not offer a true picture of the nature



of the Botalli cases in general, since patients with unusually severe cases have recently been admitted to the clinic (Fig. 9). Nevertheless, the result is noteworthy and contributes further toward strengthening the contention favoring the surgical treatment of such cases. It will be a matter of the greatest interest to follow patients with patent ductus arteriosus by means of hypoxia tolerance tests, both those already operated upon (Crafoord has sixty such cases), and above all, the cases where a comparison has been made between the conditions

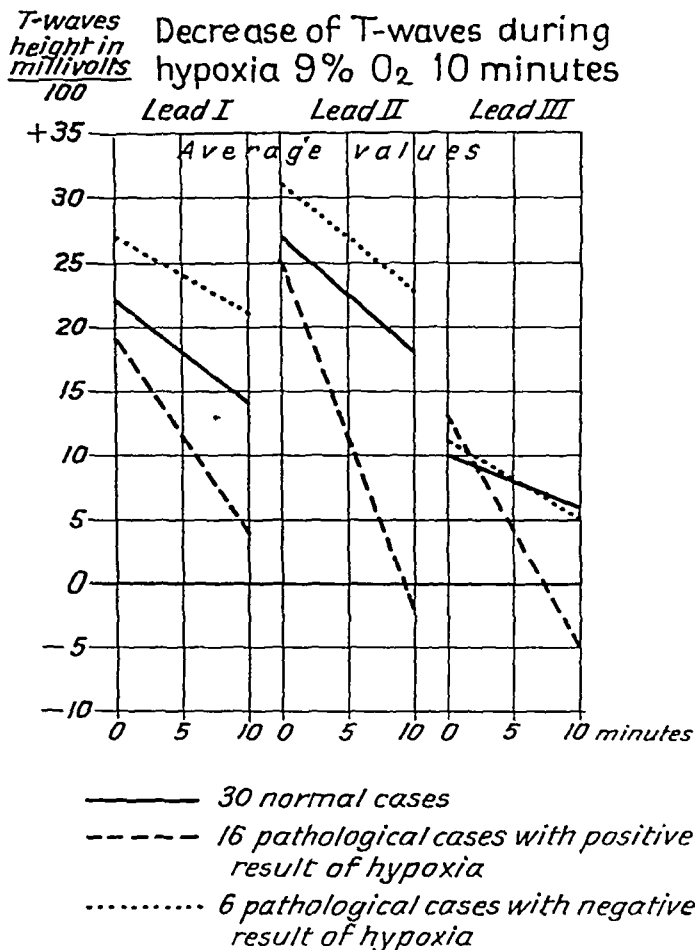


Fig. 4.

prevailing before and after the operation. At present, there are three such cases, two of which have become normal after the operation, while the third case (Fig. 9) revealed the same positive result before as after the surgical intervention. However, in the latter case only a fortnight had elapsed between the operation and examination.

Among five cases of congenital heart disease without cyanosis, only one had a positive result during the hypoxia tolerance test. One of the four negative

cases (Fig. 10) must, without doubt, be regarded as a severe congenital heart disease. The negative result indicates, in my opinion, the necessity of judging the outcome of the tolerance test otherwise than by electrocardiography or phonocardiography. It appears that several cases of cardiac diseases with dyspnea and cyanosis have reacted in a much more violent manner than the normal cases, even when electrocardiographic and phonocardiographic changes have failed to occur. For this reason, I plan to measure the oxygen content in the blood before and after the test. In this way, a better numerical manifestation of the effect of hypoxia on the body will be obtained.

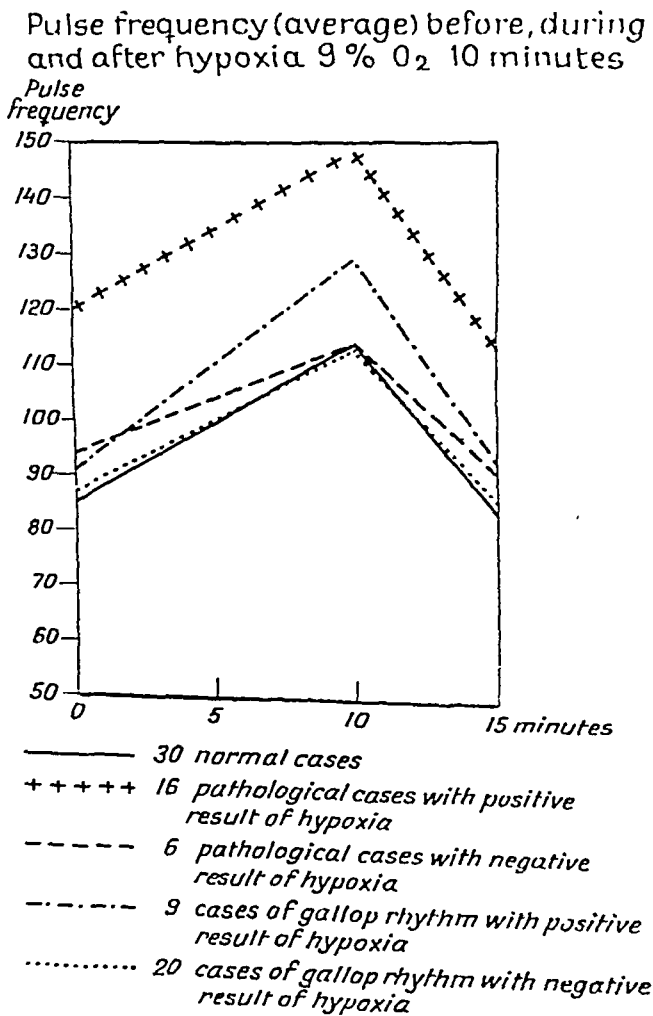


Fig. 5.

There are two positive cases in the group of postmyocarditis which have reacted during the hypoxia tolerance test by changes in the P-Q time, one with a prolongation and the other with an abbreviation of P-Q. Similar observations have been made by Larsen, but their significance is uncertain.

Finally, a few words shall be said of the gallop rhythms. This group comprises twenty-nine cases of third sound gallop which have been examined by Carlgren and will be presented in his work concerning the gallop rhythms. Only "pure" cases of gallop rhythm have been included, the cases of rheumatic carditis with simultaneous gallop rhythm having been transferred to the group of active rheumatic carditis. The "pure" gallop rhythms are, according to Carlgren, a manifestation of myocardial damage in quite a large number of cases. The result of the hypoxia tolerance test, nine positive cases (31 per cent), undoubtedly favors this assumption. Thus, it has been possible merely by means of electrocardiography to discover either a large or a small degree of latent cardiac insufficiency in almost one-third of the cases of gallop rhythm in children subjected to hypoxia tolerance tests (Fig. 11).

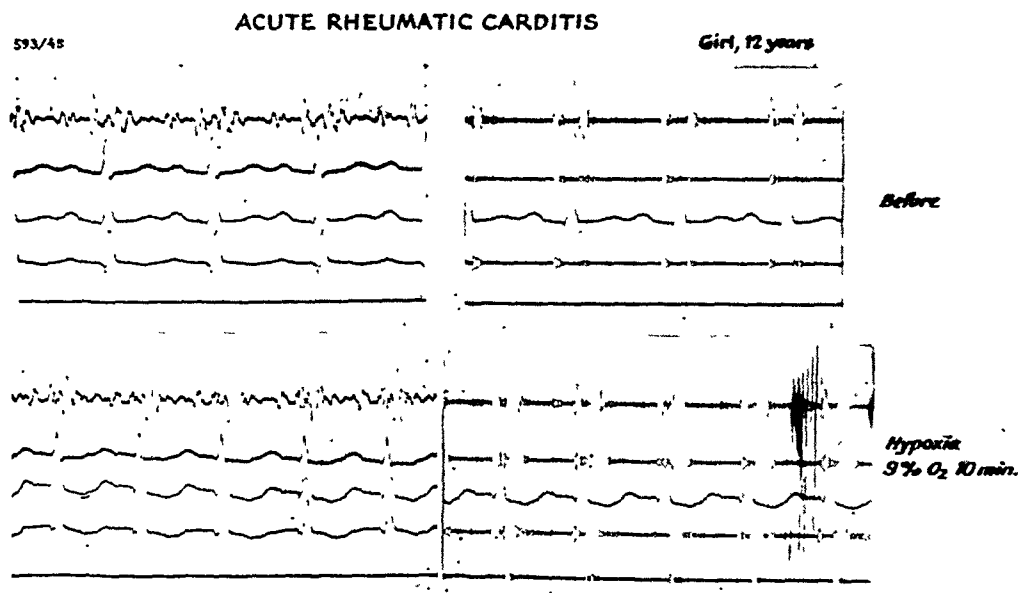


Fig. 6.

A graphic illustration of the effect of hypoxia on the T-waves is presented in Fig. 4. All the curves show a decrease during the tolerance test. In all three leads the tendency is extremely strong toward a much more pronounced decrease in cases with cardiac affections than in normal cases. In spite of the paucity of the data, it seems hardly conceivable that this difference should be due to chance.

The result of the pulse measurements is shown in Fig. 5. The original position of the pulse in the diagram will be seen to be higher in the pathologic groups than in the normal cases. The pulse increase is, remarkably enough, approximately equal in all the cases, with perhaps the exception of those with gallop rhythms which have reacted positively to the hypoxia tolerance test. In

these latter cases, a tendency toward a more pronounced increase in the pulse frequency during hypoxia may be discerned. It is possible that more comprehensive data may offer valuable information on this point. The old conception that a pulse increase after exertion would remain for a longer time in a child suffering from heart disease than in a healthy child cannot be verified by this investigation. The final value of the pulse, five minutes after the termination of the tolerance test, in all cases coincided with that originally recorded.

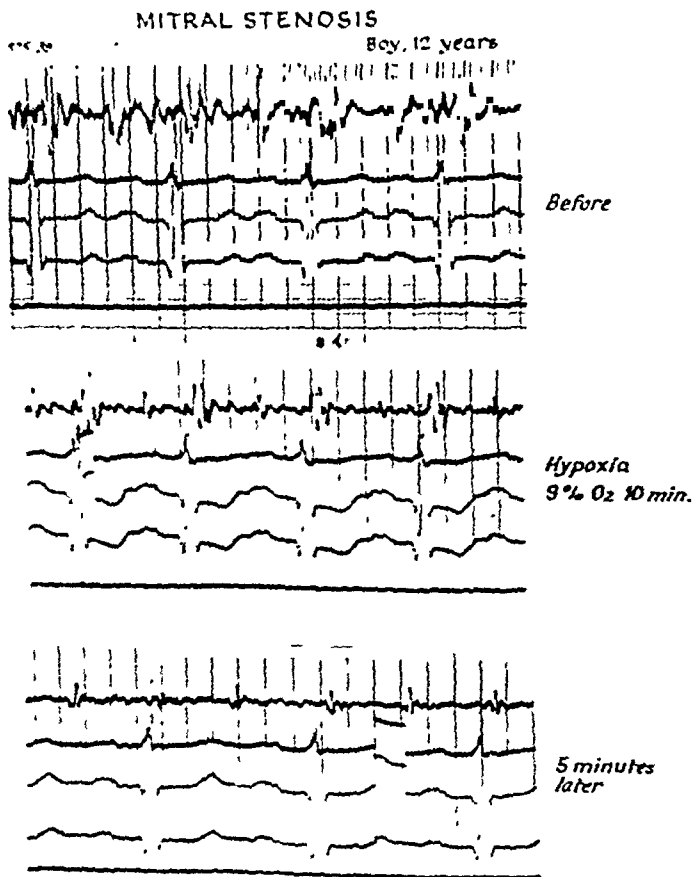


Fig 7.

Naturally, limited data of this type must, particularly in regard to the pulse, disclose large variations within the respective age groups. It is, therefore, necessary to wait for the result from a larger test series before a more comprehensive analysis can be made of the correlation between the pulse and the hypoxia tolerance test.

A few examples of cases of various heart diseases subjected to hypoxia tolerance tests are given in order to illustrate this discussion.

CASE 1.—(Fig. 6. Electrocardiogram 593/45.) The patient was a girl, 12 years old, with a diagnosis of polyarthritis and recidivistic endocarditis. In 1944, she had had chorea minor, endocarditis, and anemia. In January, 1945, scarlatina, and later, pains in the left knee. Sedimentation rate, 39 mm., which at the time of writing had fallen to 10 mm. Cardiac examination: moderate enlargement, pronounced tachycardia, gallop rhythm, and a fairly short systolic murmur of high frequency over the apex. Blood pressure: 135/80.

*Electrocardiogram* showed a sinus tachycardia of approximately 150 beats per minute. QRS complexes disclosed notch formations, and no relative axis deviation. Pronounced Q<sub>3</sub>. P-Q time of 0.15 second. T<sub>1</sub> and T<sub>2</sub> positive; T<sub>3</sub> negative with sloping S-T segments.

*Phonocardiogram* revealed a systolic murmur of 50 to 500 cycles per second. Pronounced summation sound gallop registered at 500 cycles per second disappearing when the patient was in an erect position.

*Hypoxia test* (9 per cent HO<sub>2</sub> for 10 minutes): Strongly depressed S-T intervals in all three leads. T negative in all leads.

Comparative electrocardiographic and phonocardiographic investigations, between June 26, and Sept. 25, 1945, have, on the whole, given similar results.

*Heart x-ray* (April 4, 1945): The size of the heart was 12.3 cm. in length, 9.6 cm. in breadth, and 9.5 cm. in sagittal measure. The volume equaled 510 c.c., which corresponds to 290 c.c. per square meter of body surface. There was no pathologic bulge in its contours; no changes in the aortic arch; no stasis of the lungs. The x-ray examination showed a fairly large heart without pathologic configuration.

CASE 2.—(Fig. 7. Electrocardiogram 575/39.) The patient was a boy, 12 years old, with the following diagnosis: rheumatic mitral valve disease; endocarditis recidivans (?). In July, 1939, he had angina and rheumatic endocarditis. During the next four months, a typical mitral stenosis developed. He was discharged Nov. 28, 1939, with a normal sedimentation rate. After this, he was in fairly good health until July, 1945, when conspicuous cardiac insufficiency was evident. He was readmitted with a sedimentation rate of 70 mm. Examination revealed a positive tuberculin test, but no definite signs of active tuberculosis. Heart examination showed distinct voussure, systolic and presystolic thrill over the apex, marked ictus, distinct enlargement of the heart, and prolonged systolic murmur with a short presystolic murmur over the apex. Blood pressure 130/60.

*Electrocardiogram* (Nov. 9, 1945): Sinus rhythm of 110 beats per minute; P-Q time 0.18 second; large and split P-waves. The initial complexes showed enlarged R<sub>2</sub> and R<sub>3</sub> as well as dextrogram. S-T intervals without remark. T-waves positive throughout.

*Phonocardiogram* showed a systolic murmur of 50 to 500 cycles per second; auricular sound and presystolic murmur 50 to 400 cycles per second.

*Hypoxia test* (9 per cent O<sub>2</sub> in 10 minutes): Pronounced depression of the S-T intervals in Leads II and III, and diphasic T<sub>1</sub> and T<sub>2</sub>. After 15 minutes, the findings were the same as before the hypoxia test.

Since the first electrocardiographic examination on June 21, 1939, sixteen electrocardiograms and phonocardiograms have been registered. They all show distinct signs of mitral stenosis and have, on the whole, the same character as the one described.

*Heart x-ray* (July 9, 1945): The heart was clearly enlarged, breadth 12.8 cm., 9 cm. of which were to the left. Internal thorax diameter 22.5 cm. Heart volume 875 c.c., or 840 c.c. in relation to the body surface. The left ventricle bulged markedly to the left with a pronounced pulmonary arch, and considerable backward bulge. The vascular shadows within the hilus were large and showed a distinct hilus dance.

CASE 3.—(Fig. 8. Electrocardiogram 837/45.) The patient was a girl, 4 years old, with the following diagnosis: polyarthritis, acute, and myocarditis, acute. Sudden onset with subfebrile temperature and swelling of the small joints of the hands. Sedimentation rate, 62 mm. Physical examination revealed a child in good general condition. The heart showed no enlargement, pure sounds, and regular rhythm.

*Electrocardiogram* (Sept. 20, 1945): Sinus tachycardia of 130 beats per minute; P-Q time of 0.13 second. Initial complexes were not remarkable and showed no relative axis deviation. T<sub>1</sub> was diphasic. S-T intervals were distinctly depressed in Leads II and III.

*Electrocardiogram* (Sept. 25, 1945): Sinus rhythm of 95 beats per minute; P-Q time of 0.13 second; T-waves positive throughout; and S-T intervals negative.

*Phonocardiogram* revealed a third sound gallop to 175 cycles per second; and systolic murmur of 50 to 250 cycles per second.

*Hypoxia test* (9 per cent  $O_2$  in 10 minutes): Distinct depression of the S-T intervals in Leads II and III, with diphasic T-waves.

A month later, the sedimentation rate had fallen to 14 mm., and the patient had improved.

*Electrocardiogram* (Oct. 25, 1945): Sinus rhythm of 90 beats per minute; P-Q time 0.13 second; T-waves positive throughout; and S-T intervals within normal limits.

*Phonocardiogram* still revealed a third sound gallop to 175 cycles per second.

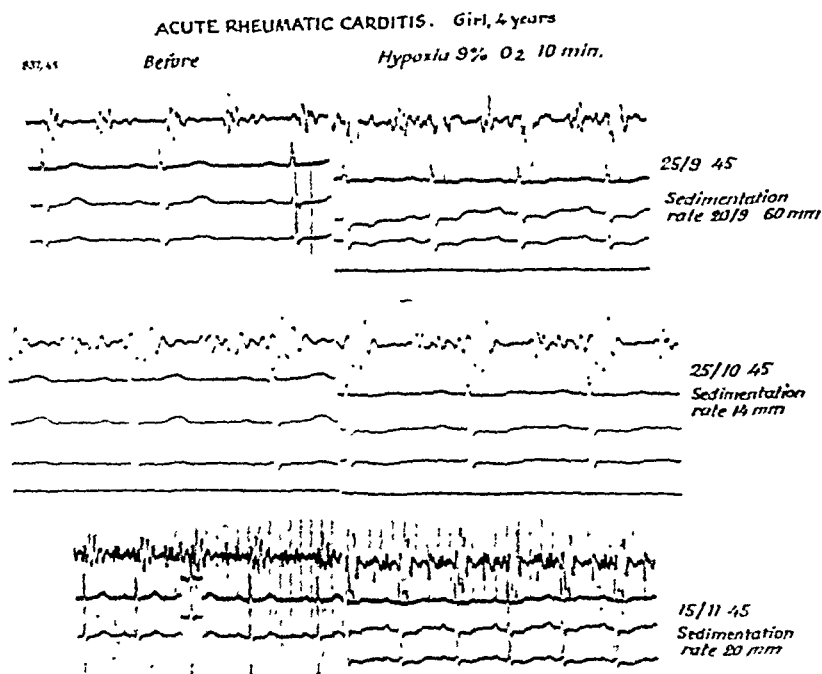


Fig. 8.

*Hypoxia test* (9 per cent  $O_2$  in 10 minutes): Less pronounced depression of the S-T intervals and only indications of diphasic T-waves. After three weeks at home, there was a further slight deterioration. The sedimentation rate was 20 mm.

*Electrocardiogram* (Nov. 13, 1945): Sinus rhythm of 100 beats per minute; P-Q time of 0.13 second, and unremarkable initial complexes showing no relative axis deviation.  $T_1$  was diphasic and the S-T intervals were within normal limits.

*Phonocardiogram* revealed a third sound gallop to 175 cycles per second.

*Hypoxia test* (9 per cent  $O_2$  in 10 minutes): Still somewhat more depressed S-T intervals and diphasic T-waves.

*Epicrisis*: Acute polyarthritis of a fairly mild type, but with changes in the S-T intervals in the first electrocardiogram, and a sedimentation rate of 60 mm. The electrocardiogram became normal after about a week. Gallop rhythm remained and the hypoxia test was positive. Hypoxia test changes appeared to follow the clinical course, first with an improvement, and then with a more positive reaction in connection with a deterioration and elevated sedimentation rate.

CASE 4.—(Fig. 9. Electrocardiogram 1004/45): The patient was a girl, 5 years old. The diagnosis was patent ductus Botalli. Since the age of 2 years, a cardiac disease had been ascertained. She had always been delicate and small. She tired on exertion and had dyspnea and palpitation. She was admitted to the hospital on Oct. 18, 1945. Her weight was 15.1 kg., and height, 107.5 cm. Cardiac examination revealed a marked thrill over the entire heart; strong ictus; a whistling systolic murmur over the apex; and pronounced, typical, continuous murmur over the pulmonary orifice. She was operated upon (Crafoord) on Oct. 26, 1945. The procedure accomplished division of the canal.

*Electrocardiogram* (Oct. 18, 1945): Sinus rhythm of 105 beats per minute and P-Q time of 0.13 second. Initial complexes showed moderate relative right axis deviation and large  $R_2$  and  $R_3$ . T-waves were positive throughout the S-T intervals were without remark.

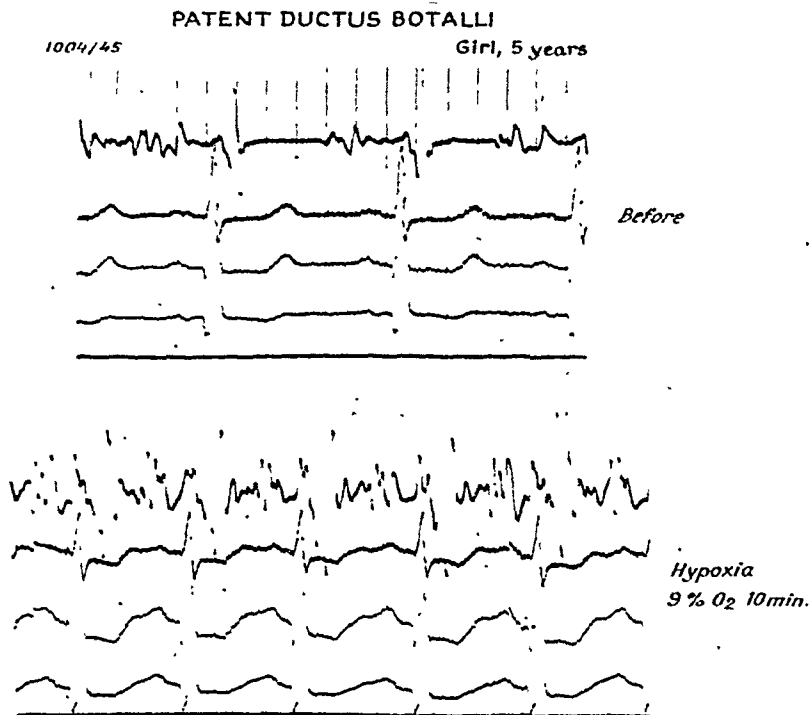


Fig. 9.

*Phonocardiogram* revealed a strongly continuous murmur of 50 to 500 cycles per second over the pulmonary orifice. A third sound gallop and systolic murmur of 50 to 500 cycles per second were noted over the apex.

*Hypoxia test* (9 per cent O<sub>2</sub> in 7½ minutes): Pronounced S-T interval depressions and diphasic T<sub>2</sub> and T<sub>3</sub>.

*Electrocardiogram* (Nov. 9, 1945, after operation): Sinus rhythm of 110 beats per minute. P-Q time 0.14 second. Initial complexes showed less pronounced dextrogram. Diphasic T<sub>2</sub>. S-T intervals slightly depressed in Leads I and II.

*Phonocardiogram* revealed a systolic murmur of 50 to 400 cycles per second. No continuous murmur.

*Hypoxia test* (9 per cent O<sub>2</sub> in 10 minutes): Pronounced S-T interval depressions and diphasic T-waves. During the hypoxia test a strong summation sound gallop was formed.

*Heart x-ray* (Oct. 19, 1945): The heart was enlarged and bulged strongly to the left and backward. There was bulging of the pulmonary arch. Frontal breadth, 11 cm., 8.5 cm. of

which were to the left of the midline. Internal thorax breadth, 17.5 cm. Cardiac volume, 340 c.c.; 520 c.c. per square meter of body surface. Enlarged vascular shadows.

Heart x-ray (Nov. 10, 1945, after operation): The heart had diminished in size, the breadth being 10.3 cm., 7.6 cm. of which were to the left. Cardiac volume equaled 285 c.c., or 430 c.c. per square meter of body surface. The posterior bulge was smaller.

Epicrisis: Patent ductus Botalli, possibly combined with a septum defect or functional mitral insufficiency. The Botalli canal was surgically ligated upon. The cardiac enlargement diminished, but the positive result of the hypoxia test remained unchanged a fortnight after the operation. The appearance of a gallop rhythm during the last hypoxia test was noteworthy. The progress of the patient will be followed with repeated hypoxia tests.

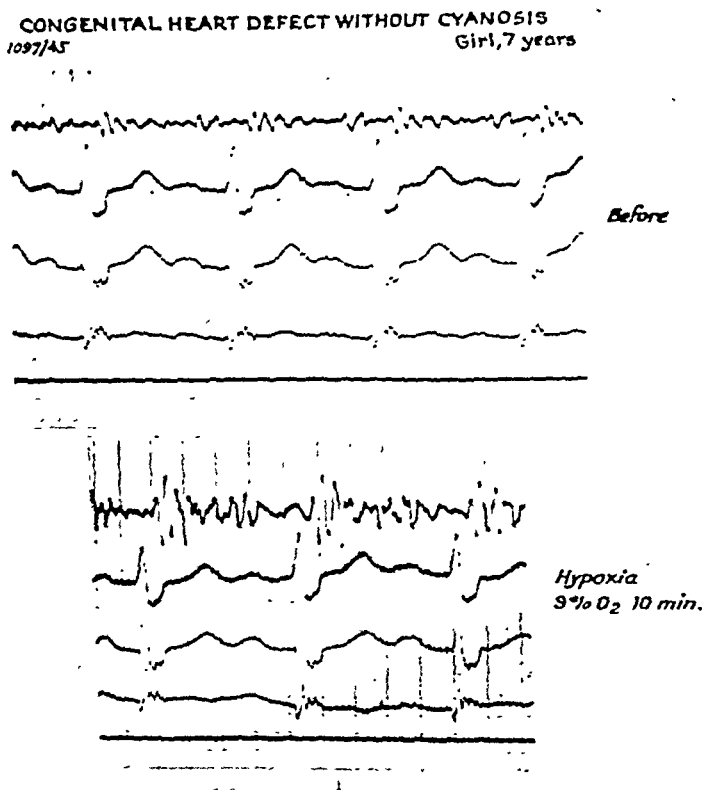


Fig. 10.

CASE 5.—(Fig. 10. Electrocardiogram 1097/45): The patient was a girl, 7 years old, with a diagnosis of congenital vitium without cyanosis (possibly a large septum defect). Since infancy, the cardiac disease had been diagnosed. The patient was thin, became out of breath, and had palpitations on exertion. There was no cyanosis. Cardiac examination: there was indication of vena-ure, a strongly systolic thrill, and an extremely marked systolic murmur was found which was maximal in the third and fourth intercostal spaces of the left of the border of the sternum.

Electrocardiogram (Nov. 1, 1945): Sinus tachycardia of 140 beats per minute. P-Q time, 0.18 second. Initial complexes showed deep S<sub>1</sub> and S<sub>2</sub> as well as notch formations. T-waves were positive throughout. S-T intervals were not definitely changed.

Phonocardiogram revealed an organic systolic murmur of 50 to 500 cycles per second. Hypoxia test (9 per cent O<sub>2</sub> in 10 minutes): Tachycardia and diphasic T<sub>s</sub>. No definite effect of the tolerance test was demonstrated.



*Heart x-ray* (Nov. 1, 1945): The heart was considerably enlarged. Breadth in the frontal picture equaled 12 cm., 7.6 cm. of which lay to the left of the midline. Internal thorax breadth, 20 cm. Heart volume, 495 c.c. or, in relation to the body surface, 550 c.c. The left ventricle bulged markedly to the left and the right contour was rounded. There was also a pronounced backward bulge. The hilus shadow with its vascular density was enlarged and diffusely delimited. Indication of stasis was found toward the bases. The examination revealed a congenital heart defect combined with an initial stasis.

*Epicrisis*: A moderately severe case of congenital vitium, possibly with a large septum defect. Initial electrocardiographic changes. Heart enlargement confirmed in the x-ray. No definite effect in the hypoxia tolerance test was noted.

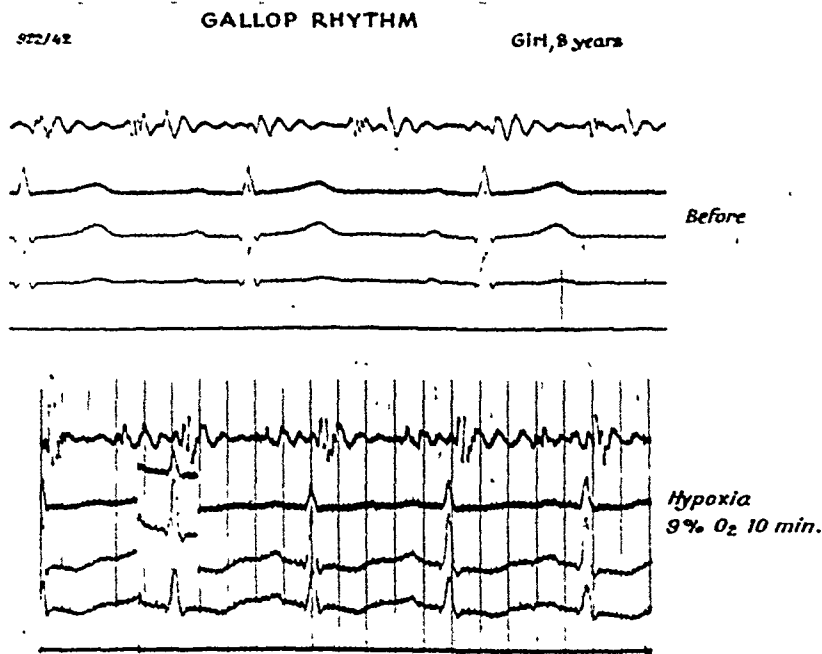


Fig. 11.

CASE 6.—(Fig. 11. Electrocardiogram 922/42): The patient was a girl, 5 years old. at the time of the first examination in November, 1942. The diagnosis was myocarditis, subacute, with a third sound gallop. In 1942, in the out patient department, a myocarditis was ascertained with a P-Q time of 0.18 second, and a pronounced third sound gallop was heard. Cardiac examination revealed a short systolic murmur and gallop rhythm at the apex. Afterward she progressed satisfactorily, possibly, however, with slight shortness of breath and fatigue at exertion.

*Electrocardiogram* (Sept. 22, 1945): Slight sinus arrhythmia of 60 to 80 beats per minute. Initial complexes were normal. P-Q time, 0.18 second. T<sub>1</sub> was faintly diphasic. S-T intervals were unremarkable.

*Phonocardiogram* revealed a faint systolic murmur of 50 to 250 cycles per second and a third sound gallop of 50 to 175 cycles per second.

*Hypoxia test* (9 per cent O<sub>2</sub> for 10 minutes): Depressed S-T segments and negative T<sub>2</sub> and T<sub>3</sub>.

*Heart x-ray* (Dec. 15, 1944): Normal-sized heart when the child was erect, but a conspicuous increase in cardiac volume when in the prone position. There was no pathologic bulge nor pulmonary stasis.

## SUMMARY

Present knowledge of latent cardiac decompensation in children is inadequate. Accordingly, an attempt has been made to come closer to the problem of the reserve forces of the child heart by means of a comparative investigation of the tolerance tests performed on healthy as well as on sick children.

For the tolerance test, respiration of air deficient in oxygen has been chosen, as applied earlier to adults by, among others, Dietrich and Schwiegk, Levy and Larsen.

A special apparatus suitable for children of all ages, as well as for adults, has been constructed. It consists of an adjustable metal ring with a hood of Plexiglas mounted on one of the ends of the bedstead. Oiled silk is attached to the metal ring which is applied to the shoulders, back, and chest of the patient. In the respiration chamber thus obtained, nitrogen and air are introduced, the oxygen content of which acquires the desired constant value after four and one-half minutes.

In the present test series, 9 per cent oxygen was used during ten minutes of tolerance testing.

The result, which is of a preliminary nature, is briefly as follows: Thirty normal cases reacted negatively. Sixteen of twenty-five cases of different heart diseases reacted positively. Seven of these cases represented active rheumatic carditis, four cases being patent ductus Botalli, one case another congenital vitium without cyanosis, one case of morbus ceruleus, and three cases of post-myocarditic conditions. In addition, a group of twenty-nine cases of third sound gallop has been subjected to the tolerance test; these patients have been examined by Carlgren and will be included in his work regarding the gallop rhythm. Nine cases (31 per cent) reacted positively, the twenty remaining, negatively. This result supports Carlgren's theory that the third sound gallop is, to some extent, to be considered a myocardial injury.

An examination of the T-waves during the hypoxia test has shown that a considerably more marked depression of the T-wave in all three leads occurred in the cases reacting positively than in those which were not affected by the respiration of air deficient in oxygen.

The pulse increased in rate during the tolerance test, both in normal and in pathologic cases. However, the data are still too limited to permit the drawing of any far-reaching conclusions.

The test, which is easy to perform, takes only 15 minutes, is free from risks, and will, no doubt, be found suitable for routine clinical work. In contrast to the working tests with registration of the cardiac effect after the completion of the exertion, the respiration of air deficient in oxygen, as in the present case, has the advantage that the heart's reaction can be recorded during the actual tolerance test. This is, in all likelihood, particularly valuable with regard to children, where the heart is characterized by a rapid mode of reaction. Thus, all the changes appearing during the hypoxia test, in normal as well as pathologic cases, had resumed their original value five minutes after the termination of the tolerance test.

For the purpose of studying more closely the effect of the hypoxia on the circulation, larger normal and pathologic series are being planned where, apart from electrocardiographic and phonocardiographic registrations and pulse recording, measurements of the oxygen-saturation of the blood will also be carried out.

*Editorial Note.*—It should be pointed out that various methods for producing anoxemia have been used for determining the efficiency of the coronary circulation and the response of the myocardium to anoxemia in disease of the coronary vessels, particularly in coronary artery occlusion.

#### BIBLIOGRAPHY

- Åkesson, S., and Malmström, G.: *Nord. med.* 25: 159, 1945.  
 Björck, G.: *Svenska lak-tidning.* 42: 1547, 1945.  
 Carlgren, L.-E.: *Acta paediat.* 32: 350, 1945.  
 Crafoord, C., Mannheimer, E., Wiklund, Th.: *Acta chir. Scandinav.* 91: 97, 1944.  
 Dietrich, S., and Schwiegk, H.: *Ztschr. f. klin. Med.* 125: 195, 1933.  
 Klemola, E.: *Acta Soc. med. fenn. duodecim, ser. B.* 32: 59, 1942.  
 Larsen, K.: *Om Forandringer i Elektrokardiogrammet hos Sunde og Syge under experimentel Iltmangel* (Danish), Kobenhavn, 1938, Enjar Munksgaards Forlag.  
 Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: *Am. Heart J.* 21: 634, 1941.  
 Lichtenstein, A., and Mannheimer, E.: *Acta paediat.* 27: 168, 1939.  
 Liljestrand, G., Lysholm, E., and Nylin, G.: *Skandinav. Arch. f. Physiol.* 80: 265, 1938.  
 Mannheimer, E.: *Acta paediat. (supp. 2)* 28: 1, 1940.  
 Mannheimer, E.: *Am. Heart J.* 21: 151, 1941.  
 Nylin, G.: *Acta med. Scandinav. supp.* 52, p. 1, 1933.  
 Pruitt, R. D., Burchell, H. B., and Barnes, A. R.: *J. A. M. A.* 128: 839, 1945.

## STRAMONIUM POISONING

### A DIAGNOSTIC PROBLEM WITH PSYCHIATRIC IMPLICATIONS

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IT IS a most hopeful sign that pediatricians are becoming more and more alert to the psychiatric implications of bizarre symptoms and ask for psychiatric consultation where such service is available. However, this not infrequently results in the presentation to the psychiatrist of cases of abnormal behavior whose etiology is organic in nature. It is not surprising that this group should include syndromes arising after the unknowing ingestion of portions of poisonous plants such as the ubiquitous *Datura stramonium*, commonly known as Jimson weed.

Despite the prevalence of this potential source of danger, it is evident from a review of the literature and a survey of the diagnostic file in an active clinic that the pathologic state known as stramonium poisoning is not commonly recognized in this country. It is the purpose of this paper to present the reports of the two cases which have been seen in the Harriet Lane Home for Children of the Johns Hopkins Hospital and who, because of the bizarre nature of their clinical pictures, came to the attention of the Children's Psychiatric Clinic.

CASE A.—J. H., a 9½-year-old Negro boy, was brought into the hospital in November, 1935, because of disorientation associated with combativeness.

Three hours prior to admission, he had appeared well except that he complained of a sore throat following a period of play out-of-doors, and displayed dysphagia when he attempted to eat.

Arousing from a very short period of sleep, he was confused, complained that he was giddy, and staggered as he attempted locomotion. His continuous stream of speech was irrelevant, he talked to persons not present, picked unseen objects out of space, and demonstrated no recognition of members of the family. Within an hour of the onset of this unusual behavior, he became "thick tongued," and exhibited fear which resulted in combativeness.

The developmental data, personal history, and family history were essentially non-contributory.

Upon physical examination, the boy was observed to be extremely restless, apprehensive, completely disoriented, and talking incessantly. The other findings of significance were markedly dilated pupils which did not react to light and accommodation, a very dry tongue, and slight motor incoordination as he walked.

The only other departure from normal was a white blood count of 12,840, with a normal differential. Examination of spinal fluid revealed no pathologic deviation.

Despite sedation, there was little reduction of delirious activity for the first twelve hours. Following a period of six hours' sleep, he awoke completely oriented and calm, and presented amnesia for the events of the preceding day.

A psychiatric examination revealed an alert, cooperative, affable boy, somewhat elated with all the attention he received. He was perfectly oriented in all three spheres. His remote memory was good as was that for recent events, except for the day of admission.

About this he stated that he knew only what he had been told, that he ate something which poisoned him, but he could not remember what. He denied any recollection of an injury, fright, or unusual experience prior to the onset of illness. At this time no evidence of either affective or organic disorder was present.

For the remainder of his four-day hospital stay, there was no recurrence of any psychic disturbance or evidence of any further physical abnormality. Just prior to discharge, the father reported that on questioning the patient's companions, it was disclosed that during the morning preceding the onset of his symptoms, the gang had sampled some "wild horsechestnuts." The patient only had found them tasty. The social worker, accompanied by the boy's companions, procured a pod from the vegetation under question. Analysis proved it to be *Datura stramonium*.

CASE B.—L. N., a 3½-year-old, Negro child, had been well except for a slight cold until about seven hours prior to admission in October, 1945. The child was found on the steps of the home complaining of inability to walk. When offered food, she seemed unable to swallow. In a short time, she complained of pains in her legs and appeared frightened. She called to her mother, but indicated by her actions that she could not see or did not recognize her. Shortly thereafter, she presented signs of delirium, spoke to and called names of people not present, picked at the carpet, carrying imaginary articles to her lips, and attempting to pick the flowers out of the fabric on the upholstered chair.

A local physician was called and, suspecting poliomyelitis, sent her to the contagion hospital. There, upon physical examination, the only abnormality discovered was a greenish foreign body in the right ear canal. This was removed. Examination of the spinal fluid revealed nothing pathologic.

Upon transfer to the Harriet Lane Home, she was totally oblivious to her surroundings. No contact could be established with the patient by either staff or parents. She was confused and in constant motion. At times her incessant activity appeared purposeless, but often she engaged in pantomime of dressing and undressing or of feeding herself. Speech was largely incoherent but incessant. She was actively resistant to examination procedures. When placed on the floor, she stood on a wide base unsteadily with body slightly inclined forward. Locomotion was slow and ataxic. However, she was not inclined to fall.

Examination revealed pupils round, regular and equal, widely dilated with sluggish light reflex. No strabismus or nystagmus was present. No other significant deviations from normal were observed during complete physical and neurological examinations.

A definite diagnosis could not be established on admission. The child was placed on sedation for the first night. The following day she was less restless, but continued to be unresponsive.

Because of a slight amount of serous drainage from the right ear (from which a foreign body was removed) the patient was placed on sulfadiazine for three days. This drug was discontinued because of oliguria. However, the eardrum showed no further signs of inflammation.

The patient was allowed to be out of bed after the fourth day. She continued to be unresponsive to the staff, wandered about in an aimless, somewhat dazed fashion, or sat quietly engaged in repetitious manipulation of a toy or her own fingers.

She recognized her parents when they visited her on the sixth day, but was considered by them to be "far away and certainly not herself." She did speak to them in a listless manner, quite contrary to her accustomed enthusiastic prattling.

For the next four days the child showed little change; she was withdrawn, noncommunicative, phlegmatic in her solitary play, rarely participating in the playroom activities with the other children. On the tenth day, psychiatric consultation was sought because it was believed that the child suffered from an affective disorder or mental retardation.

The mother, a young, alert, energetic, intelligent woman, was interviewed. Essentially the same story of the present illness was obtained. Further it was learned that the patient had always been an active child, whose development had proceeded normally. She

had never been considered nervous or presented any unusual behavior problems. She had displayed anger when frustrated, then was inclined to play alone for a while, but readily recovered from her sulkiness. She had never required severe discipline or any more attention than the other three siblings. She had always been timid and retiring with strangers, even children, but was considered a talkative child at home. Assessment of her habits revealed that she was subject to pica, and often gnawed at the varnished bed. Moreover, a 12-year-old neighbor girl reported that on the morning the patient became ill, she had observed the child chewing on a weed which she had promptly discarded. The mother was inclined to discount its significance.

During the initial psychiatric contact, the patient completely ignored most attempts on the part of the examiner to establish contact. She sat immobile except for a desultory manipulation of the fingers of the hand extended in an effort to attract her attention. With the mother, she was slightly more responsive, smiled shyly, spoke a few words in reply to the mother's questioning, and wailed when the mother departed.

A trip was made to the home where the neighbor child pointed out the remainder of the plant from which the child had eaten a pod. This was unmistakably *Datura stramonium*. This lent additional weight to the postulation that the child was victim of stramonium poisoning.

She was seen on two succeeding days and on each occasion she was in good contact. She indicated a recognition of the examiner and various members of the staff. She continued largely uncommunicative except under strong stimulus, i.e., venae puncture or a conflict with another child.

By the fifteenth day, her behavior was essentially normal; she was alert, affable, and she no longer indulged in meaningless, repetitious activity. Accordingly, she was discharged, apparently fully recovered.

#### DISCUSSION

Jennings<sup>1</sup> has contributed an exhaustive consideration of the subject of stramonium poisoning. Including a review of the literature and a concise discussion of the pharmacology, he described the classical and extraordinary features of the onset, course, and prognosis of this malady. Then he presented two cases as evidence of the ease of diagnosis and treatment when this potential source of poisoning is recognized.

In view of that excellent presentation of the many aspects of the problem, only the salient features exhibited by our two patients will receive attention herein.

The symptoms and signs observed appeared in both patients in the same order. Primarily there was inability to swallow. Disorientation soon ensued, associated with delirium in which the plucking phenomenon was a predominant feature. Widely dilated pupils which did not react to light were observed on initial examination. As the acute phase receded, amnesia replaced the delirium and in the second child, an associated perseveration was observed.

As assembled here, the symptoms would seem to lead to an unequivocal diagnosis of an organic disorder. However, the fact that they were viewed in another light merits consideration. It is not inconceivable that each of these symptoms separately might be observed in an affective disorder, but it would be rare to meet them in aggregate.

The plucking sign, so prominent a feature in both cases, is a phenomenon frequently observed in toxic delirium. When this is present one must consider the toxic state as a possible cause of the symptoms complex, despite the

temptation to the psychiatrically alert to interpret this evidence of visual hallucination as sufficient basis for labelling the state purely enigmatically "mental."

Both case histories place emphasis on the extreme apprehension and excitability exhibited by the children. Even though widely dilated pupils may be observed in a severe panic state, the persistently nonreactive dilated pupil is so constantly an incontestable sign of an organic reaction that no other explanation should be sought.

Amnesia and perseveration are aberrations of grave significance because they are indicative of organic brain damage. The appearance of these symptoms, in fact, is ascribable to transient insult to cerebral tissue by the toxic agent. In this instance, it is not the stramonium which is responsible for the symptoms. The *Datura stramonium* seed is known to contain, in addition, a variable amount of scopolamine.

It was discovered in both cases seen by us that the seeds had been swallowed. Both patients, at first, presented maniacal and delirious behavior, followed in the one case by amnesia for one day only, and in the other by amnesia associated with perseveration which continued for several days. It has been determined that the effects of the ingestion of this vegetation are varied according to the quantity and portion of the plant consumed.

The symptomatology of stramonium poisoning classically presented by standard texts is precise and definitive. This being true, one is moved to determine why the picture may be improperly evaluated.

In the first place, this disorder is so uncommonly met that the diagnostician may fail to call it to mind.

Both patients seen in this clinic dwelt in less desirable sections of the city and played, unsupervised, on overgrown lots. It is apparent that the syndrome will be observed more frequently in children who live in the areas where uncultivated vegetation is rank. It is obviously not a disease of the residents of restricted zones of the city.

It may be postulated that unwary rural inhabitants may partake of this agent and suffer transient noxious effects more frequently than is recorded. It is a common practice for the city bred to seek readily accessible medical attention at the onset of abnormal behavior in contradistinction to the conservative inclination of the agrarian to await developments.

Providing the possibility of poisoning is considered by the examiner, a cursory assessment of the history may fail to reveal any probable chance for stramonium or atropine ingestion. Therefore this consideration is pre-emptorily abandoned as not feasible because of lack of knowledge that the Jimson weed is a potential source of poisoning.

Because these symptoms, in general, may be those of a nonspecific toxic state, such as may be encountered in bacterial infections, it is not remarkable that the physician's mind-set precludes consideration of other possibilities. However, when the lack of the traditionally anticipated antecedent or concurrent clinical picture proves frustrating, the case is likely to be dismissed with an equivocal diagnosis: cause unknown.

On the other hand, the diagnosis may be missed because of the antecedent history of a chronic disease such as was thought to be present in Case B. This tempts the examiner to attribute the present symptoms to a complication of the pre-existing disease and stultifies rational, unbiased consideration of the problem in its acute and modifiable stage. This failure to exercise objective acumen derives from professional indoctrination with the time-worn diagnostic axiom, that to seek a plurality of causes for a clinical picture is deplorable.

It is understandable that in a busy clinic, scientific curiosity may be curbed when the therapeutic exigencies are abbreviated by the self-determined course of the disorder. However, the harried clinician should not feel justified in tossing into the psychiatric wastebasket all those cases which do not fit readily into his roster of organic disorders. More especially is this true when delirium is associated with other signs of neurological impairment, such as dilated pupils, inability to swallow, and ataxia. These constitute the picture of an intoxication and should spur the examiner to determine the cause, no matter how cryptic.

#### SUMMARY

The phenomenology observed following ingestion of *Datura stramonium* seeds may be incorrectly interpreted as evidence of an affective disorder. The establishment of the correct diagnosis often depends on medical sleuthing to determine the source of intoxication.

#### REFERENCES

1. Jennings, R. E.: J. PEDIAT. 6: 657, 1935.
2. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Company, pp. 460-471.



## ATTEMPTS TO ADAPT MURINE POLIOMYELITIS VIRUS TO THE CHICK

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### INTRODUCTION

ONE of the outstanding properties of the viruses belonging to the poliomyelitis group, characteristic of natural and experimental infection with human or rodent strains, is the narrow adaptation of the infectious agent to its respective host. Thus, human virus, with rare exceptions, produces disease only in man or monkeys; similarly, the corresponding mouse virus (Theiler virus) is usually virulent only for rodents. Viral strains, however, which have been experimentally acclimated from man or monkeys to rodents or from rodents to monkeys, occupy an intermediate position in that they exhibit varying degrees of monkey *and* rodent pathogenicity in consonance with the extent of the induced biologic variation. This "monopathogenicity" of poliomyelitis virus is, of course, more apparent than real. For virus-host relationship is not limited to the production of paralysis but finds its expression also in the development of subclinical lesions or in the various states of latent infection that are demonstrable by virus recovery, antibody response, resistance to reinfection, as well as protection against primary infection through interference. Yet, for all practical purposes, the restriction in the disease-producing power of poliomyelitis virus is striking<sup>1</sup> and in marked contrast to the wide pathogenic host range of other neurotropic viruses that are easily transmissible to a number of laboratory animals and grow in standard chick tissue culture media or in embryonated hens' eggs.

Previous studies with two mouse-adapted strains of human poliomyelitis virus (SK, MM)<sup>2, 3</sup> serve to illustrate what has been said. For instance, SK murine virus, which combines residual pathogenicity for monkeys with marked virulence for rodents (mouse, cotton rat, hamster, guinea pig), fails even to survive in rabbits. When propagated in tissue culture, serial passages at high titer ( $10^{-5}$ ) can easily be maintained in media prepared with embryonic mouse brain but substitution of minced chick tissue yields poor growth ( $10^{-1}$ ). No active virus can be recovered from inoculated chorioallantoic membranes and the virus is not demonstrable beyond the second egg passage. These facts are, in general, duplicated by experience with the more rodent-virulent MM virus. Thus, MM murine virus, while even less pathogenic for monkeys, is extremely potent for rodents (mouse, cotton rat, hamster, guinea pig) but at the same time altogether harmless for rabbits. The virus attains an extraordinarily

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high titer ( $10^{-9}$ ) on serial passage in embryonic mouse brain tissue culture, whereas minced chick tissue supports considerably less growth ( $10^{-5}$ ). In contrast to SK virus, however, MM virus has been carried successfully over five serial passages in the fertilized hen's egg.

The apparent ability of MM virus to maintain some rate of active propagation on chick tissue was made the subject of further study. Assuming that full adaptation could be accomplished, it was conceivable that live avian virus might be used as a protective agent against infection in monkeys with a greater margin of safety than live murine virus. Further interest in the problem was stimulated by the alleged relationship between paralytic epizootics in chickens and human epidemics of poliomyelitis, as described by Preioni<sup>4</sup> and more recently emphasized again by Rillo and Lagrotta.<sup>5</sup> The work to be reported deals: (1) with attempts to propagate MM murine virus serially in the developing chick embryo, and (2) with experiments designed to adapt MM murine virus to young chicks.

#### EXPERIMENTAL WORK

*I. Attempts to Propagate MM Murine Virus Serially in Embryonated Eggs.*—In these experiments 8- to 9-day-old embryonated eggs were inoculated by the allantoic route with 0.1 c.c. of 10 per cent MM viral mouse brain suspension or with 0.1 c.c. of chick embryo tissue culture virus. Following incubation at 35° C. for 4 to 5 days, further passages were made by transfer of undiluted allantoic fluid or of 10 per cent embryonic brain suspension to new eggs. The presence of virus was tested at frequent intervals by titrating the transfer fluids in mice intracerebrally and intraperitoneally. All in all, six attempts were made to establish MM murine virus in serial egg passage. The results obtained are shown in Table I.

The table demonstrates the extreme irregularity in the ability of MM virus, harvested from different mouse brain passages, to propagate in em-

TABLE I. PROPAGATION OF MM MURINE POLIOMYELITIS VIRUS IN SERIAL EGG PASSAGES

X- RI- ENT	SOURCE OF MM VIRUS	EGG PASSAGES									
		I VIRUS CON- TENT	II VIRUS CON- TENT	III VIRUS CON- TENT	IV VIRUS CON- TENT	V VIRUS CON- TENT	VI VIRUS CON- TENT	VII VIRUS CON- TENT	VIII VIRUS CON- TENT	IX VIRUS CON- TENT	X VIRUS CON- TENT
1	46th mouse passage ( $10^{-9}$ )	$10^{-1}$ A		$10^{-6}$ $10^{-1}$ A B	$10^{-6}$ A	$10^{-6}$ $10^{-1}$ A B	$10^{-9}$ AB	- AB			
2	61st mouse passage ( $10^{-9}$ )	$10^{-7}$ A	$10^{-5}$ A	$10^{-7}$ AB	$10^{-6}$ AB	$10^{-2}$ AB	- AB	- AB	- AB	- AB	- AB
3	62nd mouse passage ( $10^{-9}$ )	$10^{-4}$ $10^{-5}$ A B	- AB	- AB							
4	66th mouse passage ( $10^{-9}$ )	$10^{-4}$ $10^{-4}$ A B	- AB	- AB							
5	68th mouse passage ( $10^{-9}$ )	$10^{-2}$ $10^{-3}$ A B	- AB	- AB							
6	8th serial passage of chick embryo tis- sue culture ( $10^{-5}$ )	- AB	- AB								

A = allantoic fluid tested; B = brain suspension tested; AB = mixture of allantoic fluid and brain suspension. The figures given with these symbols indicate maximum potency as determined by intracerebral and intraperitoneal titration in mice.

bryonated eggs. Thus, in two experiments serial transmission could be maintained over 5 or 6 passages, whereas in three other experiments transfers did not succeed beyond the first passage. No striking difference was found between the virus content of allantoic fluid or that of embryonic brain. Noteworthy is the fact that even virus, pregrown in minced embryonic chick tissue culture at fair titer, failed to propagate in the first egg passage. The results are, therefore, in agreement with earlier observations<sup>3</sup> that MM murine virus may grow in initial transfer to embryonated eggs but cannot be maintained beyond the fifth or sixth serial passage.

*II. Attempts to Adapt MM Murine Virus to Young Chicks.*—Young chicks were injected intracerebrally (or intracerebrally and intraperitoneally) with murine virus harvested from the brains of mice paralyzed by MM mouse-passage virus. Of the injected chicks a number were kept for a period of 4 weeks to observe the development of symptoms, whereas the remaining ones were sacrificed at certain early intervals (24 hours, 48 hours, 72 hours) for the purpose of transferring intracerebrally in "blind passage" a suspension prepared from their brains or cords to new chicks. In this second transfer, and in all later transfers, the same principle was followed in that some of the injected chicks were again retained in order to permit the development of symptoms while others were killed symptomless at similar intervals for further transfer of brain or cord to new chicks. All in all, four serial chick to chick passages were thus maintained. Since earlier experience had demonstrated the frequent presence of *Salmonella pullorum* infection in young chicks purchased on the market, the chicks used in these experiments were supplied by a dealer from a tested hatchery. The animals varied in age between 1 and 7 days.

In the first experiment a total of 15 chicks received intracerebrally 0.06 c.c. of a 10 per cent viral mouse brain suspension (twentieth mouse passage). Six chicks were sacrificed for "blind passage" after 24, 48, and 72 hours, respectively, while 9 chicks were retained to study the primary infection. In the latter group of 9 animals, 6 chicks died with indefinite symptoms within 3 to 5 days; one chick developed, on the twenty-fifth day after inoculation, a paralysis of the right leg; and 2 chicks survived without any symptoms. Passages of brain and cord suspension from the 6 dead chicks to new chicks were negative, except for one transfer which caused paresis in 1 of 3 injected chicks after an incubation period of 24 days. This condition, however, could not be reproduced in a subsequent passage. Similarly, it proved impossible to transmit to new chicks the paralysis produced in one chick by the original virus inoculation. There was also available for further study another group of 15 chicks representing animals which had been retained from "blind passages" carried out at the 24, 48, and 72 hour cycles. All of these animals remained well, excepting 6 chicks, i.e., 3 chicks from the 24 hour cycle, first or third transfer; 2 chicks from the 48 hour cycle, third transfer; and 1 chick from the 72 hour cycle, second transfer. These 6 chicks showed the same paretic or paralytic leg involvement after incubation periods varying from 17 to 24 days.

In no case was it possible to further transmit this condition to new chicks. The chicken paralysis is illustrated in Figs. 1 and 2.

Although definite paresis or paralysis was observed in a total of 8 inoculated chicks, the nature of this condition remained uncertain, particularly since it proved nontransmissible in serial chick passages. Was it due to (a) nutritional deficiency, (b) intercurrent bacterial infection, (c) latent virus disease, or (d) was it etiologically connected with the activity of MM virus? The first two possibilities can probably be excluded since the chicks were fed an adequate standard diet and blood as well as tissues were uniformly found sterile by bacteriologic examination. The chance that we were dealing with a latent infection of avian encephalomyelitis seems also remote even though the clinical picture of the observed paralysis resembled in many ways the spontaneous



Fig. 1.



Fig. 2.

Fig. 1.—Chick with paresis of left leg following injection with MM murine poliomyelitis virus in the second chick passage (transfer from dead chick of first passage.)

Fig. 2.—Chick with paresis of left leg following injection with MM murine poliomyelitis virus in the second chick passage (transfer from blind first passage, twenty-four-hour cycle).

virus disease described by Olitsky.<sup>6</sup> For paralysis was never produced in control experiments in which chicks were injected with normal mouse brain, normal chick brain, or heat-killed MM virus, including serial blind passages. On the other hand, certain facts provide circumstantial evidence to suggest that the chicken paralysis was actually induced by MM virus. Thus, murine virus of low potency could regularly be recovered by transfer to mice from nervous tissue, occasionally also from blood and spleen, of chicks following primary intracerebral inoculation with MM virus during the first 96 to 120 hours after infection even though brains harvested from subsequent chick passages were uniformly free from any mouse-pathogenic agent. Occurrence of a viremia in these chicks, irrespective of the absence or presence of symptoms, compares closely with similar observations described by Hammon, Reeves, and Burroughs<sup>7</sup> for chickens, following injection of Japanese B encephalitis virus, and leaves

little doubt that systemic infection had taken place. Furthermore, neutralization experiments (intraperitoneal injection of mice with virus-serum mixtures) were carried out with one serum from a paralyzed chick and with two sera from nonparalyzed chicks, all of which had been injected with original live mouse virus. All three sera were capable of inactivating large doses of MM virus (100,000 paralytic doses); however, doubtful (10 paralytic doses) or no neutralization occurred with five sera collected from asymptomatic passage chicks. Normal chicken serum failed to neutralize the virus. When present, virucidal antibodies could be demonstrated at undiminished titer in repeated tests for as late as two months after the original infection. The available data, therefore, strongly suggest that at least the symptoms observed in infected chicks of the first passage were caused by activity of MM virus.

The above experiment was repeated: (1) with another specimen of MM murine virus (thirty-third mouse passage), (2) with MM murine virus grown in tissue culture prepared either with minced embryonic mouse brain (fifty-first passage) or with minced embryonic chick brain (twelfth passage), (3) with virus grown in embryonated eggs (first passage or fourth passage). The results were: (1) Among a total of 40 chicks inoculated with MM viral mouse brain not a single chick was observed with paralysis; however, three sera collected from symptomless chicks after primary infection with MM virus again contained large amounts of virucidal antibodies (10,000 to 100,000 paralytic doses neutralized). No paralysis was observed in "blind passage" chicks and no antibodies were present in the serum of such animals. (2) Among a combined group of 29 chicks inoculated with either mouse embryonic or chick embryonic tissue culture virus not a single chick was observed with paralysis. Neutralization tests demonstrated the presence of small amounts of antibody (100 paralytic doses neutralized) in the sera of two of these animals. (3) Allantoic fluid with a virus content of  $10^{-1}$ , transferred from the first egg passage, failed to produce any symptoms in 3 chicks, but allantoic fluid with a virus content of  $10^{-6}$ , transferred from the fourth egg passage, produced paralysis in 1 of 3 chicks on the third day after intracerebral inoculation. The animal was killed on the same day and a brain-cord suspension was transferred to mice and new chicks. Even though all the mice died with typical paralysis following injection with high dilutions ( $10^{-5}$ ), the disease could not be transmitted to new chicks.

#### DISCUSSION

The data presented in this paper bring into sharp relief, once more, the extreme dependency of poliomyelitis virus in its growth requirements upon a given host. While it is possible, on occasion, to force a mutation\* in the infectious agent so that it will propagate in the tissues of another unrelated host, in most instances such attempts result only in abortive infections. Almost always the experience leaves the virus with a markedly depressed parental

\*The term "mutation" is used here in a general sense to designate a biological process which causes the virus to display new properties such as enhancement of virulence or ability to multiply in foreign tissues with or without the production of lesions. It is a reasonable assumption that these new properties make their appearance because of hereditary selection of one variant at the expense of the other in a virus entity which originally contained both variants in fixed proportions.

virulence with no compensatory gain in foster virulence. Experimentally, and perhaps also epidemiologically, such transfers will therefore cause merely isolated cases of disease in the new host which fail to transmit in series.

There is close agreement between the results obtained in this work and the trend of similar observations made in attempts to adapt murine poliomyelitis virus (SK strain) from albino mice to guinea pigs. Only seldom are the conditions sufficiently favorable to permit the establishment of a fixed avian strain of virus.<sup>8</sup> Nor do they differ very much from the problem involved in the successful transfer of simian virus to rodents or of rodent virus to monkeys.<sup>9</sup> What deserves special emphasis, however, is the fact that chick tissue, commensurate with its grade of biologic differentiation, apparently offers uneven chances for viral adaptation. Thus, fair growth may be secured in serial transmission of tissue culture media which utilize minced embryonic chick brain as a substrate; the intact embryo in the egg, on the other hand, supports viral propagation only at a poor rate over a measured series of passages. In the hatched chick, finally, virus activity reaches merely the threshold of latent infection; development of paralysis is rare and in no case has it been possible to establish a fixed avian strain of virus. It should be pointed out, however, that, unlike the rabbit, the chick may ultimately prove not to be a completely refractory host since active virus has always been recovered from animals of the first passage.

#### SUMMARY AND CONCLUSIONS

1. Experiments in which embryonated eggs were inoculated with MM murine poliomyelitis virus demonstrated the possibility of viral propagation in initial transfers, but active virus could not be recovered beyond the fifth or sixth serial egg passage.

2. Inoculation of young chicks with this strain of virus, as a rule, produced no paralytic symptoms. However, in several instances the infected birds developed flaccid paralysis of the legs after a variable incubation period. No fixed avian strain of virus could be established in subsequent serial chick passages.

3. Irrespective of the absence or presence of symptoms, primarily injected chicks harbored active virus in brain, blood, and spleen and their serum contained specific neutralizing antibodies.

4. The reported data illustrate the flexibility in the pathogenic properties of the virus when passage is attempted from one host to another.

#### REFERENCES

1. Schwab, J. L., Woolpert, O. C., and Hudson, N. P.: *J. Infect. Dis.* 72: 97, 1943.
2. Jungeblut, C. W., and Sanders, M.: *J. Exper. Med.* 72: 407, 1940.
3. Jungeblut, C. W., and Dalldorf, G.: *Am. J. Pub. Health* 33: 169, 1943.
4. Jungeblut, C. W.: *J. Exper. Med.* 81: 275, 1945.
5. Preioni, C.: *Semana méd.* 48: 1149, 1941; 51: 132, 1944.
6. Rillo, A. B., and Lagrotta, A.: *Enfermedad de Heine-Medin (Parálisis Infantil)*, Buenos Aires, 1944, Editorial Olivé, pp. 125-146.
7. Olitsky, P. K.: *J. Exper. Med.* 70: 565, 1939.
8. Hammon, W. McD., Reeves, W. C., and Burroughs, R.: *Proc. Soc. Exper. Biol. & Med.* 61: 304, 1946.
9. Jungeblut, C. W., Feiner, R. R., and Sanders, M.: *J. Exper. Med.* 76: 31, 1942.
9. Jungeblut, C. W.: *Am. J. Pub. Health* 33: 1227, 1943.

# NEWER AGENTS IN THE TREATMENT OF EPILEPSY

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EPILEPSY is slowly emerging from the doghouse of professional bewilderment and defeat. The increasing speed of its release can be measured by the intervals of time which separate the discovery of effective antiseizure drugs. From the caveman to bromide, many thousand of years; from bromide to phenobarbital, seventy-five years; from phenobarbital to diphenylhydantoin, twenty-five years; from diphenylhydantoin to trimethyloxazolidine dione, eight years. At this threefold rate of acceleration, we should have yet another effective remedy by the spring of 1948!

Today we may consider, first, the therapeutic agents recently acquired, and, second, those which we may have in the future—given the needed research brains and money.

## PREVENTION

Prevention has priority over remedial treatment and applies to both genetic and acquired causes. As for genetic prevention, electroencephalography is of potential aid in the detection of a transmitted predisposition to seizures. Brain wave tracings provide at least one leg for eugenics to stand on and give to the present-day physician a certain degree of confidence when he is asked to advise about marriage and children.<sup>1</sup> Prevention of certain acquired conditions (birth injuries, encephalitic-producing infections, traumas) may allow even a predisposed child to remain outwardly and clinically "normal." Finally, the potential epileptic, one with subclinical electroencephalographic seizure discharges, may be given drug therapy for the prevention of possible seizures.

## PSYCHOLOGICAL-SOCIAL TREATMENT

Emotional and psychological wreckage is strewn about the long-standing public horror of epilepsy. Fear of public exposure, of expulsion from school, of losing friends, and opportunities for future marriage and employment, prey on parents and on teen age patients alike.

Psychological treatment has received a great impetus, and physicians a needed lay support, through the educational activities of the recently organized American Epilepsy League.\* The skeleton is out of the closet. The word epilepsy can be spoken aloud in the consulting room and printed in papers and magazines. Warm hope is gradually ameliorating the chill atmosphere of popular despair.

## NEUROSURGICAL TREATMENT

Physical treatment by means of neurosurgery is not new, but recent progress has been made in matching the symptoms of a seizure with the responsible areas of the brain, in delimiting this epileptogenic focus, and in removing it with minimal damage to the neighboring tissues.<sup>2, 3</sup> Neurosurgeons are now leaving

From the Children's and Infant's Hospital of Boston. Read before The American Academy of Pediatrics, Region I, New York City, April 3, 1946.

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the scar alone, and instead are excising normal-looking brain tissue, possibly distant from the scar, which harbors the abnormally discharging neurons. In this work of detection the electroencephalogram plays a significant role.

#### THE ELECTROENCEPHALOGRAPH

In many specialties, laboratory techniques have lifted treatment to new levels of precision and success. Think of the orthopedist without the roentgen ray, the syphilographer minus the Wassermann test, the cardiologist deprived of the electrocardiograph. For bewildered physicians who diagnose and treat epilepsy, the electroencephalograph is a gift, via Germany, from the gods. Graphic recording of the electrical activity of the surface of the brain gives six-fold assistance.

1. Epilepsy is manifested as a disturbance in the rate and the voltage of electrical potentials of the brain.

2. The area of the cortex which is "firing" seizure discharges can often be identified, either from electrodes placed on the scalp or, more precisely, on the cortex. Stimulation of the exposed cortex with a current too weak to produce clinical symptoms will set up telltale electrical discharges in the epileptogenic area, thus identifying the portion of the brain to be removed.<sup>5</sup>

3. Each of the three main types of clinical seizures is accompanied during the seizure by a different type of high voltage electrical waves; fast (grand mal); slow (psychomotor); alternately fast and slow (petit mal).

4. In seizure-free periods, the quality and quantity of abnormal waves helps to measure the severity of the epilepsy and, on repeated tests, the success of therapy.

5. The pattern of the waves, their frequency and voltage, whether normal or abnormal, can be altered by chemical means, for example by the acidosis produced by ketosis or by mental activity.

6. Evidence is dawning of specific chemical therapy for specific abnormal wave formations. The alternate three-per-second dart and dome formation is particularly susceptible to acid-base changes and to medication with trimethyl-oxazolidine dione.

#### CHEMICAL THERAPY

Our principal interest as physicians centers about the possibility of inhibiting or perhaps abolishing seizures by chemical means. Convulsions and epilepsy are predominantly problems of infancy and childhood. Pediatricians (Geyelin, Peterman, Helmholtz, Talbot, Gamble) were the first to take the fad of fasting into the laboratory, convert it to the ketogenic diet and analyze the reasons for its success in controlling seizures. Unfortunately, the attention span of pediatricians proved to be unduly short, as is suggested by the fact that of the last 652 articles on the subject of epilepsy, only 10, or less than .2 per cent, have appeared in journals devoted to the problems of children.

Out of these early dietary and metabolic studies came demonstration of the inhibiting effect not only of ketosis but of acidosis, however produced. These findings have brought scientific explanation and backing to a policy of keeping

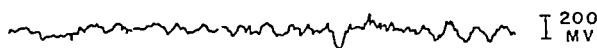


epileptics in circulation, actively busy in sports or in climbing the educational ladder. The carbonic acid and the lactic acid which result from muscular and mental work are as important as drugs in the inhibition of seizures. Not stagnation, but productive activity is the password to a life with fewer seizures and more happiness. Laboratory demonstration of the triumph of mind over matter is shown in the accompanying figure. When this patient was sitting idly with eyes closed, alternate dart and dome discharges of petit mal were almost continuously present. When her eyes were open and she studied a picture on the wall, the abnormal discharges disappeared. This phenomenon has been pointed out before.<sup>4</sup>

#### EYES CLOSED-MIND IDLE



#### EYES OPEN-STUDYING PICTURE



#### EYES CLOSED-ATTENTIVE



#### EYES CLOSED-MIND IDLE



— SECOND —

Fig. 1.—Effect of brain activity on petit mal seizure discharges. During the first of the examination, the patient, J. W., sat with eyes closed and mind idle. Spike and wave formations (first line) were almost continuous. With eyes open and studying a picture on the wall (second line), the abnormal waves disappeared. They did not recur when the eyes were closed but she was attentive to conversation (line three). On sitting for half a minute with mind vacant, the petit mal dysrhythmia returned. (last line). Recordings were from the left frontal area. The signal at the right marks 200 microvolts, the line at the bottom one second of time.

#### DRUG THERAPY

The benefit derived from the ingestion of a few decigrams of a selected chemical may exceed that of a laboriously sustained dietary ketosis. Furthermore, a seemingly slight alteration in the structural formula of a compound may benefit a different type of seizure or produce different side effects. With the coming of new drugs, the physician's prescription may be tailored to fit the particular type of seizure involved.

Three relatively new drugs may be named.

1. *Sodium Diphenylhydantoin* (phenytoin or dilatin sodium) is now eight

years old but many practitioners do not secure maximum benefit for their patients because of inadequate dosage or failure to follow their patients closely. The gap between the amount of the drug which gives freedom from seizures and that which produces annoying muscular incoordination or other disturbing side effects may be a narrow one. Trial of this drug cannot be considered a failure unless the point of tolerance has been reached. Pediatric literature tells little about the therapeutic and toxic effects of this drug in children as contrasted with adults. It is the drug of choice for grand mal or psychomotor seizures, although phenobarbital may be given first trial. Psychomotor seizures are common enough in children, though usually called petit mal or behavior disorder. Diphenylhydantoin is most likely to stop psychomotor seizures, but petit mal seizures are increased as often as relieved.

2. *Methylphenylethylhydantoin*. This drug (called mesantoin by Sandoz, the manufacturers) is not yet on the market. The results obtained by my colleague, Harry L. Kozol, in the treatment of 115 patients are reported elsewhere.<sup>5</sup> In a group of 30 patients, personally supervised, six, or 20 per cent, have obtained far greater relief from methylphenylethylhydantoin than from other drugs. An advantage over diphenylhydantoin is the absence of the side effects of muscular incoordination or hyperplasia of the gums. Disadvantages are the more frequent skin reactions and greater sedative effect. Convulsive but not petit mal seizures are aided. Because of side effects full dosage needs to be approached gradually. It is dispensed in 0.1 Gm. tablets. Older children may be given 0.2 to 0.6 Gm. daily. Methylphenylethylhydantoin is welcomed as a possible substitute for phenobarbital or diphenylhydantoin when the lack of therapeutic results or toxic reactions requires a change.

3. *Trimethyloxazoladine dione*. The trade name used by Abbott is Tridione. This drug, which has been reported<sup>6</sup> is a surprising addition to our armamentarium. The surprise is on three counts.

First, is the drug's relative specificity for seizures of the petit mal triad, seizures not usually influenced by the anticonvulsants. These three sorts of seizures are petit mal (or pykno-epilepsy), myoclonic jerks, and akinetic (loss of posture) seizures. Looking at these seizures from the level of the cortex, they are changes of potential characterized by an alternate spike and wave formation of the electroencephalogram. Pediatricians should especially welcome this medicine, for members of the petit mal triad are disproportionately prevalent in children and youths.

The second surprise is the high proportion of patients relieved, and the pronounced reduction in the number of seizures. The sudden disappearance of transient blackouts or falls which recur many times every day is, of course, more dramatic, although no more welcome, than the disappearance of a monthly or a bimonthly convulsion. A patient with petit mal will, say, have 300 or 400 one month and, on medication, none the next. The average grand mal patient rid of this many convulsions would be seizure free for several years.

Third, is the unexpected and as yet unexplained photophobia which accompanies the use of tridione in about one-third of the patients. Young children seem to be relatively immune to this annoying side effect.

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Third, is the unexpected and as yet unexplained photophobia which accompanies the use of tridione in about one-third of the patients. Young children seem to be relatively immune to this annoying side effect.

During the past two years, we have given tridione to 145 patients of all ages, who have a history and, almost without exception, electroencephalographic evidence of one or more of the petit mal triad. All of these patients were having daily seizures, from several to scores of attacks every day. None had received important or prolonged benefit from the use of other drugs.

Thirty-five of these patients also had frequent grand mal. In addition, tridione was given to 32 patients who had frequent grand mal or psychomotor seizures without complicating petit mal. The accompanying tabulation gives the percentage of persons receiving different degrees of benefit for the two groups of seizures, first, those of the petit mal triad, and, second, seizures classed as grand mal or psychomotor.

RESULT OF THERAPY	PETIT MAL TRIAD PER CENT	GRAND MAL OR PSYCHOMOTOR PER CENT
Seizure free	33	6
Free of more than 75 per cent	30	6
Somewhat improved	21	8
Unchanged	13	35
Worse	3	45
Total patients	145	67

Therapeutic results in these two groups were opposite. Eighty-four per cent of patients with petit mal were improved; 80 per cent of those with convulsive or psychic seizures were unimproved. Just as the use of diphenylhydantoin may increase the frequency of petit mal, tridione may augment grand mal seizures when they occur frequently in patients having petit mal.

These observations do not mean that tridione cannot be used in patients having a combination of petit mal and convulsions. In the presence of frequent grand mal, the medication which has proved most effective in controlling these must be continued. An initial increase in grand mal when tridione is first given may not continue. If it does, tridione must be stopped, since petit mal seizures, in comparison with grand mal, are relatively innocuous.

As for control of the perplexing psychomotor seizures, tridione used alone seems of little effect. De Jong<sup>7</sup> reported relief of psychomotor seizures in six patients when tridione was added to dilantin or phenobarbital therapy. Occasionally I have encountered good results from combined therapy, but as yet the incidence of remissions is hardly beyond that which may occur spontaneously.

The long-term effects of therapy are of course unknown. Some patients with brain pathology or with especially bad or persistent cerebral dysrhythmia, after a period of improvement, may experience a gradual return of seizures which may or may not be countered by an increase of dosage. Patients whose seizures and dysrhythmia are relieved usually display improvement in disposition and in mental alertness. Also, several who were rendered seizure free have discontinued therapy without, as yet, a return of symptoms. In judging the ultimate prognosis, and the safety of discontinuing medication, repeated electroencephalograms are of value.

Other conditions which cause trouble or even force temporary discontinuance of tridione therapy are widespread rash, increased irritability or overactivity, gastric symptoms, and photophobia. Photophobia is countered by the use of dark glasses: On the appearance of a rash, medication must be stopped until the rash clears, then resumed with small and gradually increasing doses. A plastic agranulocytic anemia with death occurred in one patient. A capsule of tridione contains 0.3 Gm. Conservative daily dosage is as follows: infants, 1 capsule; children 2 to 4 years of age, 2 capsules; 5 years and above, 3 capsules. Amounts may be increased to a maximum of three times those named.

These three drugs, dilantin, mesantoin, and tridione increase the range and effectiveness of therapy far beyond what we dreamed of ten years ago. But modern weapons of war are no better than pitch forks in the hands of the untrained and the uninterested. New medicines call for careful reading of the literature and conscientious trial by the practicing physician.

#### OTHER AND FUTURE TREATMENTS

The list of drugs and of measures which in the last few years have been reported as anticonvulsant, is impressive in length, if not in demonstrated value. Examples are: mebaral, delvinal sodium, di propyl oxazolidine dione, glutamic acid, thiamine, amphetamine sulfate, caffeine, atropin, acetylcholine, azosulfamide, neoprontosil, brilliant vital red, desoxycorticosterone, dehydration, and even induction of convulsions by injections of a convulsant drug or by electric shock. Back of these drugs which have been given at least tentative clinical trial lies a backlog of dozens of chemicals which have proved of anticonvulsant value in animals but await evaluation in man.<sup>5</sup>

Even though these or other drugs do not promise immediate help for any substantial portion of the epileptic population, any treatments which are even partially effective, may, like bent twigs in a forest, point the path to the physico-chemical mechanism of seizures.

We know what it is that we need yet to know—the abnormal metabolism of the neurones of the brain which causes them to discharge excessively or the abnormal rate regulating mechanism which results in synchronous or dysrhythmic discharges. Certain possible stepping stones to needed knowledge are visible. The respiratory quotient of the human brain is unity, of the many sugars, it burns only glucose, and in the approximate theoretical amount, 1.34 mg. per c.c. of oxygen. The chief products of glucose oxidation, carbon dioxide, is, together with pH, the chief stabilizer of the electrical potentials of the brain. When brain potentials are stable, the brain functions better and, if epileptic, it gives off fewer seizure discharges.

These data<sup>9, 10</sup> derived for the most part from a study of conscious healthy young men, whose electroencephalograms are normal, offer controls for observations of the metabolism of the brains of epileptics, and the influence on its metabolic processes of sugar, of oxygen, and of calcium, of fever, and of synthetic drugs which are known to influence seizures or cortical potentials. We require more knowledge of the inward workings of the nerve impulse, and the relation of seizures to the chemical mediation of nerve impulses across synaptic barriers. We must learn the role of endocrine glands, the balance in the nervous

system of potassium and sodium and the effect of vitamins and of penicillin (the last a convulsant when applied directly to the brain).

The problems of epilepsy are many—but surely not insoluble. If so much has been learned with so meager an expenditure of brains and money, what could be accomplished by a serious, concerted attack? In the study of child health which your academy is undertaking, the epileptic children should be moved out of their present obscurity into the front row, into a position of attention commensurate with their numbers and the devastating nature of their symptoms.

As to the most pressing immediate needs, I repeat the recommendations made before the Congressional Committee investigating possible governmental aids for the physically handicapped.<sup>11</sup>

1. \$250,000 a year as grants in aid for research.
2. Establishment of a diagnostic-research-training center or centers.
3. Schools with proper medical supervision for the education and training of young patients of normal intelligence.
4. Education of the public to modern conceptions of epilepsy.

The proposed new Children's Center of Boston is planned to meet its responsibility as regards the second item on this list by the creation of a diagnostic-research-training center which will fill the triple purposes of a consultative service for hard-pressed pediatricians, research into some of the many unexplored problems of epilepsy, and a center of teaching and training for medical students, doctors, nurses, and social workers.

Treatment is more than judicious prescription of pills and capsules, or the skillful use of a scalpel. It means new discoveries. It means prevention. Treatment deals with fear and shame, with education and employment, with the instruction of patients and parents, professional staffs, and the world at large. Earlier I mentioned the fact that less than 2 per cent of articles on convulsions and epilepsy appear in pediatric journals. You, of course, agree that this is too small a share for physicians who are constantly confronted with convulsions, either single or recurrent. No pediatric problem is more intriguing or, when solved, more rewarding.

#### REFERENCES

1. Lennox, W. G.: Marriage and Children for the Epileptic, *Human Fertility* 10: 97, 1945.
2. Penfield, W. and Erickson, T. C.: *Epilepsy and Cerebral Localization*. Springfield, Ill. Charles C Thomas, 1941.
3. Walker, Major E.: (personal communication).
4. Lennox, W. G., Gibbs, F. A., and Gibbs, E. L.: Effect on the E.E.G. of Drugs and Conditions which Influence Seizures, *Arch. Neuro. and Psychiat.* 36: 1236, 1946.
5. Kozol, H. L.: Mesantoin in the Treatment of Epilepsy, *Am. J. Psychiat.* To be published.
6. Lennox, W. G.: The Treatment of Epilepsy, *M. Clin. North America* 1114-1128, 1945. *Ibid*: The Petit Mal Epilepsies, Their Treatment with Tridione, *J. A. M. A.* 129: 1069, 1945.
7. DeJong, R. N.: Effect of Tridione in the Control of Psychomotor Attacks, *J. A. M. A.* 130: 565, 1946.
8. Merritt, H. H., and Putnam, T. J.: Experimental Determination of Anticonvulsive Activity of Chemical Compounds, *Epilepsia* 3: 51, 1945.
9. Gibbs, E. L., Lennox, W. G., Nims, L. F., and Gibbs, F. A.: Arterial and Cerebral Venous Blood: Arterial-Venous Differences in Man, *J. Biol. Chem.* 144: 325, 1942.
10. Gibbs, F. A., Gibbs, E. L., Lennox, W. G., and Nims, L. F.: The Value of Carbon Dioxide in Counteracting the Effects of Low Oxygen, *J. Aviation Med.* 14: 250, 1943.
11. Aid for the Epileptic, Committee on Labor—Subcommittee on Aid to the Physically Handicapped, H. Res. 45, Part II, Epilepsy, May 24-25, 1945.

# IMMUNIZATION AGAINST WHOOPING COUGH

## A CLINICAL STUDY

D. LAPOINTE, M.D.\*

QUEBEC, CANADA

CANADIAN statistics show that in 1944, scarlet fever was responsible for 115 deaths; poliomyelitis, 119; measles, 239; diphtheria, 309; and whooping cough, 336. During the same period in the United States, whooping cough has caused the death of more infants in the first two years of life than measles, diphtheria, poliomyelitis, and scarlet fever combined. On the basis of statistical evidence, however, it is difficult to appreciate the lasting and debilitating effects—postpertussis bronchiectasis, cerebral lesions—which so frequently follow an attack of pertussis. The high mortality rate, as well as the high incidence of sequelae which have been observed, would therefore appear to indicate that whooping cough is a disease against which therapeutic and prophylactic measures have either been ineffective or poorly understood.

At the present time, the treatment of whooping cough is being directed essentially toward the use of either rabbit or human serum, both of which have produced favorable results. In the realm of prophylaxis, it has long been admitted that isolation in the absence of other preventive measures is neither effective nor practical. At the time when the child is most highly infective, that is, in the catarrhal stage, it is often impossible to diagnose the disease clinically. While the cough plate method may provide a valuable diagnostic aid, it is not always reliable nor are bacteriologic laboratories always at the disposal of the attending physician. Active immunization would therefore seem to provide the only practical means of prevention.

In the early years following the discovery of *Hemophilus pertussis* by Bordet and Gengou (1906), an attempt was made to immunize children with a vaccine made from these organisms. In 1914, this vaccine was accepted by the Council on Pharmacy and Chemistry of the American Medical Association. During the following years, so many unfavorable reports appeared in the literature that the Council declared in 1931, that pertussis vaccines were no longer acceptable. In the same year, however, it was observed that the antigenicity of a bacterial vaccine was very high when such a vaccine was prepared from freshly isolated strains of *H. pertussis*.

Reports published in the last ten years have tended, for the greater part, to demonstrate the effectiveness of this newer vaccine. Among the authors who have contributed extensively to the study of this vaccine are: Madsen, in the Faroe Islands, Sauer, Kendrick, and Eldering.

A critical analysis of various publications on pertussis immunization would seem to point out that the measure of protection which is provided by bacterial vaccines ranges from 60 to 90 per cent. This variation has often been accounted

Translation of a lecture delivered before the meeting of the Association des médecins de Langue Française de l'Amérique du Nord, at Quebec City, June 13-16, 1946.

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for on the basis of such variables as the numerical count of organisms in the vaccine, the dosage and interval between doses, the number of injections, the possibility of an outbreak of paraptussis, and the particular resistance of certain individuals to *H. pertussis*.

Failure to provide protection in certain individuals led some investigators to believe that the toxin of the organism (which was first described in 1909, by Bordet and Gengou and later demonstrated by Teissier, Lawson, Evans, and Kimball) might be concerned with the etiology of the disease. In 1940, an endotoxin was isolated by Strean who, in collaboration with Grant, succeeded in demonstrating that the material was antigenic in rabbits. A quantity of rabbit serum, even as much as 0.016 c.c. was sufficient to protect a mouse against 2 M.L.D. of toxin. In later studies on the antigenic quality of this endotoxin, Strean produced a vaccine which contained 15 billion organisms per cubic centimeter combined with 150 provisional units of pertussis endotoxoid. This combined vaccine\* has been under clinical trial at La Creche St. Vincent de Paul since 1942. We have observed the same local and general reactions which we ordinarily find when using the bacterial type of Sauer.

La Creche is a foundling home which houses 650 children whose ages range from birth to 4 years. The children are kept in dormitories measuring 36 by 14 feet in groups of 36. The dressing rooms and playrooms are common quarters so that the children come in close contact one or more times daily. Owing to crowded facilities, isolation is impossible in the event of contagious diseases.

Since 1942, 150 children have been vaccinated against whooping cough every year. All received three injections of 2 c.c. at one-month intervals. Because some of the children were adopted and some died before adoption, there remained only 100 vaccinated individuals in a total enrollment of 650 at the onset of an outbreak of whooping cough on July 1, 1945. At this time, the vaccinated individuals as well as the nonvaccinated children were together in the same dormitories. From then on, the immunized children were closely watched with regard to onset, frequency, severity as well as duration of paroxysms (Table I).

TABLE I. CONSOLIDATED REPORT ON OUTBREAK AT LA CRECHE

	NUMBER OF CHILDREN	PER CENT
Enrollment July 1, 1945	650	
Group previously immunized	100	
Group with a history of pertussis	35	
Controls	515	
Incidence of pertussis in nonvaccinated group	450	87.3
Incidence of pertussis in vaccinated group	10	10.0
Complications in nonvaccinated group		
Bronchopneumonia	6	
Deaths from bronchopneumonia	3	
Mediastinal emphysema	2	
Deaths from mediastinal emphysema	2	
Complications in vaccinated group	0	
Deaths in vaccinated group	0	

\*Provided through the courtesy of Ayerst, McKenna & Harrison Limited.

*Dormitory No. 319.*—On Sept. 6, 1945, it was observed that cases of whooping cough were scattered throughout the dormitory so that contact appeared to be unavoidable. Under existing circumstances, we felt justified in instituting such measures as would indicate when an immunized individual came into contact with a pertussis case in order to test the degree of the immunity in the vaccinated group. To this effect, in this dormitory where there were eleven immunized children, we introduced between September 6, and November 7 (72 days) three children who had contracted the disease at the beginning of the outbreak and presented classical symptoms.

1. B. M. entered September 6, and removed October 18.
2. C. N. entered September 18, and removed November 17.
3. A. M. entered October 9, and removed November 17.

None of the immunized children developed symptoms of pertussis following 72 days of observation. It was not until December 29, or 42 days after the end of the observation period in Dormitory No. 319, that 2 children, P. L. and O. L., became ill with pertussis (Table II). R. L., another member of the group of eleven vaccinated children, began to whoop on Jan. 8, 1945, or 52 days after the period of observation had been completed. In these three children, the attack of the disease was severe in one, moderate in a second, and mild in a third. The remaining eight children resisted the disease.

TABLE II. HISTORY OF IMMUNIZED CHILDREN DEVELOPING PERTUSSIS

SUBJECTS	AGE (MONTHS)	ONSET OF DISEASE AFTER LAST INJEC- TION (MONTHS)	DURATION OF DISEASE (DAYS)	TOTAL NUMBER PAROXYSMS	VOMITING	CYANOSIS	SEVERITY OF DISEASE
V. V.	29	4	20	18	5	2	Mild
L. R.	32	4	33	28	6	14	Moderate
M. S.	31	8	19	100	6	0	Moderate
G. P.	34	6	22	112	2	0	Moderate
L. R.	32	6	27	98	2	0	Moderate
P. L.	16	5	32	150	8	18	Severe
O. L.	15	5	30	122	0	10	Mild
R. L.	15	6	24	110	13	12	Moderate
G. G.	19	6	21	60	3	0	Mild
M. B.	24	10	15	57	0	7	Mild

On Jan. 3, 1946, of the group of 100 previously immunized children, 21 who had not had the disease were given a fourth injection of 2 c.c. After two months' observation, none had contracted the disease.

## COMMENTS

We want to emphasize the fact that in our clinical experiments, in view of the large number of children, the immunized individuals were exposed to pertussis for a longer period of time than is possible in a family and to much more massive infection. The children were literally submerged by the infection. In spite of these unfavorable conditions, not more than 10 per cent of the immunized children contracted pertussis and none with complications. The attack was

mild in four, moderate in five, and severe in one. It was difficult to determine to what extent immunization modified the disease. It is important to note, however, that in the nonimmunized group there were six cases of severe bronchopneumonia with death in three cases; two deaths resulted from mediastinal emphysema. Moreover, the group of immunized children who did not develop pertussis resisted massive infection for approximately 110 to 120 days. As a matter of fact, in Dormitory No. 319, where contact was rigorously controlled and where the eleven immunized children were exposed to massive infection for weeks, it took at least 114 days for the disease to develop in three children while the remaining eight were completely protected. This observation would appear to indicate that all individuals are not protected to the same degree by active immunization against pertussis. After verifying this observation clinically we decided to give a fourth injection to 21 previously immunized children who had not developed pertussis.

Considering the unfavorable conditions which rendered the children subject to certain exposure, we believe that the results obtained with the use of the combined bacterial vaccine and endotoxoid were excellent. We could not prove conclusively, however, that the endotoxoid increased the immune response because we did not have a control group immunized with bacterial vaccine alone. At the moment, it must remain an open question, but we expect to have the answer in the future since we anticipate experimenting with the two types.

While we believe that definite immunity is conferred by the injection of 6 c.c. of endotoxoid-vaccine, there seems to be no doubt that a booster dose of 1 c.c. given annually or every second year would give almost complete protection, thereby reducing materially the mortality and morbidity rates.

#### SUMMARY

Of 650 children at La Creche St. Vincent de Paul, 100 were immunized with pertussis endotoxoid-vaccine. In an outbreak of pertussis in this institution only ten of the immunized children developed pertussis and none developed complications or died.

In the controls, 450 became ill with the disease, six developed bronchopneumonia of which three died, and two died of mediastinal emphysema.

#### REFERENCES

1. Felton, H. M., and Willard, C. Y.: *J. A. M. A.* 126: 29, 1944.
2. Singer-Brooks, C.: *J. PEDIAT.* 14: 25, 1939.
3. Miller, J. J., Jr., and Faber, H. K.: *J. A. M. A.* 112: 1145, 1939.
4. Perkins, J. E., Stebbins, E. L., Silverman, H. F., Lembeke, P., and Blum, B. M.: *Am. J. Pub. Health* 32: 63, 1942.
5. Daughtry-Denmark, L.: *Am. J. Dis. Child.* 63: 453, 1942.
6. Strean, L. P.: *Canad. M. A. J.* 42: 525, 1940.
7. Strean, L. P., and Grant, G. A.: *Canad. M. A. J.* 43: 528, 1940.
8. Strean, L. P., Lapointe, D., and Dechene, E.: *Canad. M. A. J.* 45: 326, 1941.
9. Strean, L. P.: *J. Bact.* 43: 80, 1942.
10. Strean, L. P.: *J. Bact.* 45: 72, 1943.
11. Lapointe, D., and Strean, L. P.: *Laval méd.* 7: 265, 1942.

## IDIOPATHIC LIPEMIA

BERTHA M. LEVY, M.D.

OKLAHOMA CITY, OKLA.

THERE have been reported in the literature only six cases of idiopathic lipemia. Bürger, and Grütz<sup>2</sup> reported the first two cases in 1932; Goodman, Shuman, and Goodman<sup>3</sup> and Chapman and Kurney reported a case and included a post-mortem examination; Franklin; Opitz;<sup>4</sup> and Holt. Aylward, and Timbres<sup>1</sup> also reported cases, the latter being very completely worked out. All the cases had in common, lipemia and hepatosplenomegaly. In four cases it was stated that improvement occurred on a low-fat diet.

This purpose of this paper is to present another case of this unusual disease.

H. H., an 8½-year-old child, was first seen in May, 1944, with the history of having had nausea and vomiting intermittently throughout the previous winter. For the past month he had had abdominal pain, but the nausea and vomiting had ceased. The pain, which was almost constant, began around the umbilicus and radiated to the right flank and the right lower quadrant. Pain was increased on the ingestion of food but not on drinking water. The patient was thought to have had fever the night before he was seen.

There was a history of hard stools since infancy. For this he had taken Agarol. Past illnesses included purulent otitis media, pertussis, rubeola, and varicella.

At examination the child weighed 51 pounds and was alert and active. Dental caries was present. The remainder of the examination was normal except the abdomen, where there was considerable tenderness with moderate muscle spasm on the right, especially the right upper quadrant. The liver was enlarged about 2½ inches below the costal margin and extended to the left of the midline. The spleen was palpated to just above the level of the umbilicus. Blood count at that time was 14,200 white cells, neutrophiles, 78 (filamented 57, nonfilamented 21); lymphocytes, 16; and monocytes, 6. When he was seen again two days later in consultation with a surgeon, the examination was unchanged except that the abdomen was no longer tender. As he had felt well during those days it was decided to temporize, and Syntropan was prescribed for pain.

Two weeks later he was seen again. He had had no pain until the morning of the examination. Syntropan was given then without effect. Abdominal examination was unchanged. Blood count was rechecked and revealed 10,800 white cells: neutrophiles, 73 (filamented 53, nonfilamented 20); lymphocytes, 23; eosinophiles, 2; and monocytes, 2. The technician at that time remarked that the blood was very peculiar and that she had made the count three times. Venous blood was withdrawn and looked like melted strawberry ice cream. When it was allowed to clot, the serum was milky. On refrigeration of the supernatant fluid, approximately one-half the fluid was fat and one half serum. Blood studies and other studies done before and during hospitalization are recorded herein.

The patient was placed on a fat-free diet and got along very well except for one time when he ate fried chicken and ice cream. This precipitated an attack of severe pain following which he vomited and had a few loose stools. Over a period of several months there was a decrease in the size of the liver and of the spleen. Then he began to resume a full diet. He felt well, but his liver and spleen enlarged somewhat. Ophthalmoscopic studies showed lipemia retinalis.

Because of technical difficulties it was impossible to do serum fat determinations or to send specimens elsewhere for laboratory examination. The amount of fat was roughly estimated by the relation to the total fluid after removal of the clot and refrigeration of the fatty serum.

On the first and subsequent examinations until a low-fat diet was instituted, the lipoids were about one-half. When the diet was adhered to they dropped to one-fifth. When the patient resumed a full diet they became approximately one-third.

Plasma cholesterols on several occasions varied from 250 to 329 mg. per cent. The values were the same before and after fat extraction with ether. Fasting blood sugars were repeatedly normal. Exton's glucose tolerance gave a rise from 73 mg. glucose, fasting, to 98 mg. in thirty minutes and 105 mg. in one hour. There was no glycosuria. Stool examination showed occasional neutral fat globules and no fatty acids or soaps. Vidal test was negative; gastric analysis, normal; bone marrow smears, normal; skull film, G-I series, and excretory urograms were normal.

Blood taken from the mother, father, and a half-brother (mother's child) appeared normal. The sister of the patient had about one-fourth fat. She has never had any complaints. Abdominal examination was unsatisfactory.

#### REFERENCES

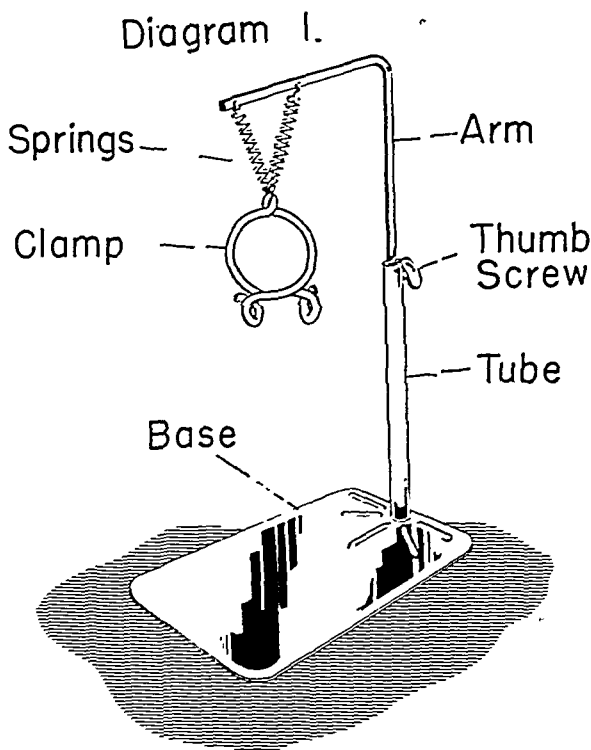
1. Holt, L. E., Jr., Aylward, F. X., and Timbres, H. G.: Bull. Johns Hopkins Hosp. 64: 279, 1939.
2. Burger, M., and Smitz, W.: Arch. f. Dermat. u. Syph. 166: 542, 1932.
3. Goodman, M., Schuman, H., and Goodman, S.: J. Pediat. 16: 596, 1940.
4. Opitz: Deutsche med. Wchnschr. 61: 88, 1935.

# A PRACTICAL DEVICE TO HOLD THE NURSING BOTTLE DURING BOTTLE FEEDING

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SANTA MONICA, CALIF.

ALTHOUGH much progress has been made on the problem of the type and cleaning of nipples and bottles, little practical progress has been made in improving the position of the bottle and nipple during bottle feeding.

Hoffman<sup>1</sup> noted that during the sucking motion in breast feeding, the mandible was lowered and pushed forward and the muscles of the tongue, cheeks, lips, and pharynx were called upon for a combined and vigorous action. Through the muscular pull a healthy stimulation is exerted on the bones of the jaw, mouth, and nose.



Saxl<sup>2</sup> states that when a proper nipple is placed in the child's mouth, its base should press against the maxilla causing the less-well developed mandible to be thrust forward into the correct position before the mouth is closed for sucking.

However, whether the child is on the attendant's lap, or lying on his back in bed with the bottle being held by hand, the attendant's hand usually soon tires and the bottle sags to the child's chest. The weight of the bottle tends to press against the mandible instead of the maxilla thus hindering the for-

ward movement of the mandible. Also, if the bottle is dropped to a horizontal position the child will suck quantities of air.

Grulee<sup>3</sup> deplores the fact that in many hospitals, due to shortage of attendants, it is a custom to elevate the bottle on a pillow and allow the child to get the food in the best way he can. This method is also used in many homes where the mother is too busy to hold the bottle. In this position the insufficient inclination of the bottle allows the child to swallow a lot of air after the level of the liquid is below the orifice of the nipple. Another disadvantage of this

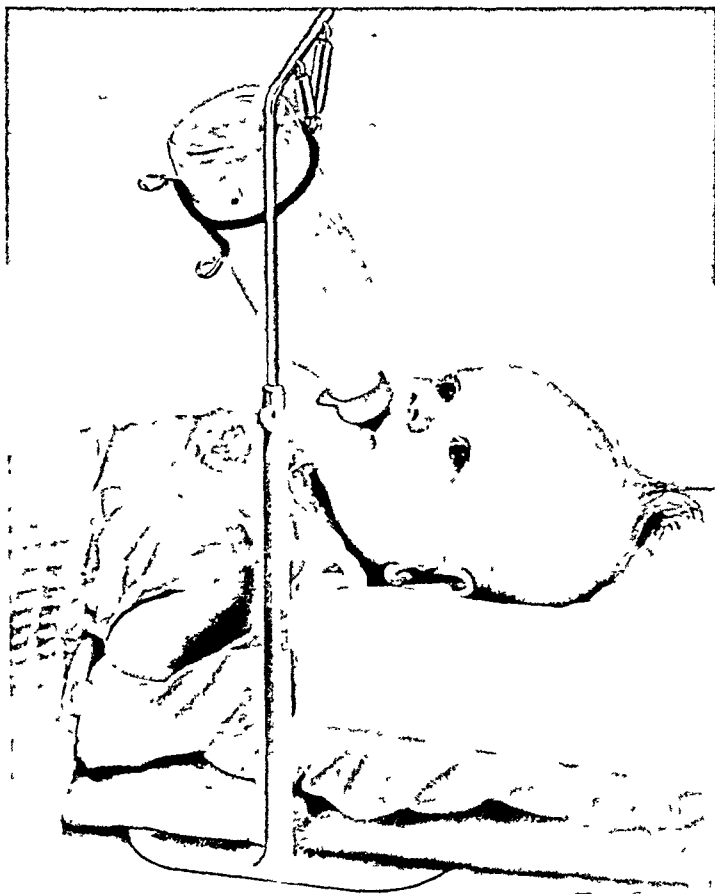


Fig. 1.

method is that the child is in a horizontal position which hinders the eructation of swallowed air, whereas the semupright position would facilitate the escape of swallowed air during feeding. Moreover, feeding the child on his left side or right side adds gravitational effects to the passage of swallowed air and food into the stomach which has certain disadvantages that the upright or semi-upright positions tend to avoid.

Since sufficient attendants in the present-day hospitals are a rarity on account of expense and other factors, and labor-saving devices, sometimes

superior to manual procedures, are one of the advantages of the so-called American way of life, a satisfactory device to hold the nursing bottle in a proper position seems desirable for both attendant and child.

Hence the description of a device that has been in service here for more than five years and has proved satisfactory in use. It is sufficiently simple for the average attendant to accustom herself to, yet it is adaptable to almost any type of feeding location in the home and in the hospital.

Fig. 1 is a pictorial representation of the device and Fig. 2 shows the device in use.

Specifications are: The base should be 6 by  $9\frac{3}{4}$  inches of 16 gauge sheet steel. To the base is welded a tube  $\frac{1}{4}$  inch inside diameter and  $9\frac{1}{2}$  inches high, and at its upper end is welded a 10 by 32 nut to take a thumb screw. The part of the tube above the thumb screw is flattened to make a half-round opening. The arm is of  $\frac{3}{16}$  inch square steel rod. This prevents the arm from rotating when placed in the half-round opening of the tube. The horizontal part of the arm is 7 inches long and the vertical part  $9\frac{3}{4}$  inches. Attached to the arm are two small coil springs  $2\frac{1}{4}$  inches apart; and below, the coil springs are connected to the clamp. The clamp is of piano wire .100 inches thick and is covered with blood pipette rubber tubing.

A pillow and /or folded blanket should be placed under the shoulders and head of the child and over the base of the device to incline the body up to about a twenty-five-degree angle.

With the child in position as in Fig. 2, the nipple of the filled bottle is placed in the child's mouth and the clamp is opened slightly by pressing the pressure pads together. Slide the clamp over closed end of the bottle about one-third the distance from closed end of the bottle. Release pressure pads and clamp will grip the bottle automatically. The height of the arm is raised until there is the slightest tension in the coiled springs, then tighten thumb screw.

If a child is fed in the same place at each feeding it is seldom necessary to adjust the thumb screw after the first feeding. The clamp alone will compensate for slight variations of position. For the child old enough to sit in a high chair the device will hold the nursing bottle satisfactorily if that feeding location is desired.

The child may let go of the nipple when he tires of nursing and after a rest period it should be replaced. The average child of 4 months or older will reach up and replace the nipple dangling over his head into his mouth by himself when ready to resume nursing.

The child should be held over the shoulder or allowed to sit erect after the feeding in order to belch as is done after a breast feeding but it will be found that much less eructation is necessary than if the child were fed horizontally.

#### REFERENCES

1. Hoffman, K. F.: *Deutsch. Zahnärztl. Wchnschr.* 1933. (Quoted by Saxl.)
2. Saxl, N. T.: *Pediatric Dietetics*, Philadelphia, 1937, Lea & Febiger.
3. Grulee, C. G.: *Infant Feeding*, ed. 4, Philadelphia, 1922, W. B. Saunders Company.



# American Academy of Pediatrics

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## Proceedings

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### REPORT OF THE MEETING OF THE EXECUTIVE BOARD OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., JUNE 7, 8, 1946

A meeting of the Executive Board was held at the Palmer House, Chicago, on Friday and Saturday, June 7 and 8, 1946. The first session was called to order at 10 A.M., Friday by the President, Dr. Jay I. Durand. There were present: Drs. J. I. Durand, Lee Forrest Hill, Edgar E. Martmer, Marshall C. Pease, Paul W. Beaven, Hugh K. Berkley, James W. Bruce, Roger L. J. Kennedy, Félix Hurtado, George F. Munns, Warren W. Quillian, Vernon W. Spickard, Oliver L. Stringfield, and Clifford G. Grulee.

The following applicants were elected to Fellowship:

#### *Region I*

Harry Bloch, Brooklyn, N. Y.  
Amy Breyer, Hartford, Conn.  
John K. Brines, Wellesley, Mass.  
John W. Buckley, Bridgeport, Conn.  
Philip S. Chasin, Forest Hills, L. I., N. Y.  
Charles Henry Classen, Rosemont, Pa.  
Harry E. Cohen, New York, N. Y.  
Robert Downing Cox, Worcester, Mass.  
Howard Reid Craig, New York, N. Y.  
Joan Neilson Daly, Forest Hills, L. I., N. Y.  
Charles H. Deichman, Morristown, N. J.  
Francis C. DeLorenzo, Newark, N. J.  
Lester Jacob Greenberg, Far Rockaway, N. Y.  
John E. Gundy, Rye, N. Y.  
Arthur P. Keller, Ellwood City, Pa.  
Anthony J. Maffia, New York, N. Y.  
James H. Maroney, Summit, N. J.  
Frank Louis Marting, Schenectady, N. Y.  
Charles D. May, Boston, Mass.  
Charles A. Murphy, Stamford, Conn.  
Hugo Neuhaus, Freeport, L. I., N. Y.  
Gertrud C. Reyersbach, Boston, Mass.  
Irwin Schiff, Brooklyn, N. Y.  
Lawrence M. Shapiro, New York, N. Y.  
Dorothy L. Shindel, Philadelphia, Pa.  
Harry Shwachman, Roxbury, Mass.  
Joseph Frankle Siegel, Washington, Pa.  
Sydney E. Sinclair, Williamsport, Pa.  
Lois Miller Smedley, Forest Hills, L. I., N. Y.  
W. Russell Smith, New York, N. Y.

Samuel Stone, New York, N. Y.  
 Elizabeth Ufford, Port Washington, N. Y.  
 Helen M. Wallace, New York, N. Y.  
 Mortimer Wolf Weber, New York, N. Y.  
 Gibson J. Wells, Baltimore, Md.  
 Jean Wells, West Hartford, Conn.  
 Gladys Winter, Teaneck, N. J.  
 Murray Woronoff, Keyport, N. J.

*Region II*

Katherine Anderson, Winston-Salem, N. C.  
 William R. Britton, Montgomery, Ala.  
 Harold W. Buchner, Oklahoma City, Okla.  
 Jacob A. Danciger, Memphis, Tenn.  
 James P. Hanner, Atlanta, Ga.  
 James Harrell Harris, Marshall, Texas  
 Paul Hogg, Newport News, Va.  
 Weston M. Kelsey, Winston-Salem, N. C.  
 Selby V. Love, Louisville, Ky.  
 Philip Magrish, San Antonio, Texas  
 Joseph H. Patterson, Gastonia, N. C.  
 J. Cyril Peterson, Nashville, Tenn.  
 David William Van Gelder, Baton Rouge, La.  
 Robert B. Warfield, Lexington, Ky.

*Region III*

Edward W. Beasley, Chicago, Ill.  
 Meryl Myron Fenton, Detroit, Mich.  
 Herbert William Fink, Detroit, Mich.  
 Harold F. Flanagan, St. Paul, Minn.  
 Morton J. Freedman, Peoria, Ill.  
 Lawrence Eddy Goldman, Clayton, Mo.  
 Werner K. Gottstein, Chicago, Ill.  
 George Martin Guest, Cincinnati, Ohio  
 Evelyn Smith Harris, St. Paul, Minn.  
 Stanley L. Harrison, St. Louis, Mo.  
 Louis Edward Heideman, Detroit, Mich.  
 Kenneth E. Humphrey, Alton, Ill.  
 William Wayne Lockwood, Urbana, Ill.  
 William G. Motel, Chicago, Ill.  
 Joseph N. Rappaport, Evanston, Ill.  
 Eleanor J. Rector, Akron, Ohio  
 Henry F. Saunders, Cleveland, Ohio  
 Lloyd Marlow Simonson, Sheboygan, Wis.  
 Matthew Michael Steiner, Chicago, Ill.  
 Walter Stoeffler, Indianapolis, Ind.  
 Robert H. Trimby, Lansing, Mich.  
 James R. Wilson, Chicago, Ill.

*Region IV*

Robert H. Alway, Salt Lake City, Utah  
 John A. Anderson, Salt Lake City, Utah  
 Virginia Murray Cobb, Carmel, Calif.  
 Paul T. Hahman, San Francisco, Calif.

Clement J. Molony, Beverly Hills, Calif

Sidney Rosin, Los Angeles, Calif

Robert A. Trombley, Albuquerque, N. M

Dr. Frank L. Fletcher of Ann Arbor, Michigan, was reinstated at his request

The resignation of Dr. Newton T. Saxl of New York was accepted.

Upon application, Dr. L. R. DeBuys was granted Emeritus Membership

### Report of the President

It is customary for the president to give a brief report of the activities of the Academy since the last meeting

The most notable achievement has been the financing of the Child Health Study and the energetic manner in which the project is getting under way

The Executive Board and the members of the Academy are very grateful to the National Foundation for Infantile Paralysis, Inc., Mead Johnson and Company, M and R Dietetic Laboratories, Inc., Carnation Company, Pet Milk Company, the Field Foundation, and the Lederle Laboratories, Inc., for providing funds which enable us to meet the rather staggering budget with which we were presented at the Detroit meeting

Dr. Sisson and his committee and the very efficient director, Dr. John P. Hubbard, now have the work well under way in all but a few states. The pilot study in North Carolina is daily proving its value in furnishing local committees and state chairmen with valuable techniques and methods of procedure. The scope of the study is being enlarged to cover pediatric education. After the survey is completed, the Academy should be the agency to carry on child health work wherever its need has been demonstrated. I would suggest that a Post Survey Planning Committee be named at our next meeting.

One of the pleasant experiences of the early months of my administration has been the willingness of almost all whom I have asked to serve on committees and as state chairmen. The state chairmen particularly have undertaken the job knowing that it involved much work of a kind not congenial to many of them.

The plans for an Academy sponsored Pan American meeting have been upset by the decision to hold an International Pediatric meeting in 1947. Had the members of the Executive Board been informed that plans for this meeting were under way, this confusion could have been avoided. The Board must decide how to unscramble this situation.

The Secretary and the Academy Office are doing a very worthwhile job in placing physicians released from service in residencies and equivalent positions. The survey made by Dr. McQuarrie's committee has been helpful. There are many more candidates than positions offered. I believe that there are more hospitals which could offer such residencies with benefit to themselves and the men seeking instruction.

### Report of the Secretary

Perhaps the matter which most of us have at heart at the present time is the question of the legislation in Washington. It is only by insistence that Dr. Wall was able to appear before the Committee, as you will see by his subsequent report. We, of course, have no information as to what may happen, but we have done what we could to prevent what most of us feel would be a calamity to the children of the United States.

As recommended by the Secretary and voted by the Executive Board at the last meeting, it was decided to do away with memberships in Latin America which required only \$5.00 a year dues. There were forty-six of these members who were on the \$5.00 list. All but one of these from whom we have heard has decided to continue on the revised \$10.00 list so that it seems now that only a small proportion of the members in Latin America will fail to avail themselves of the change. This has materially altered the situation with respect to the Latin American members in that it has done away with one of the most costly efforts, by discontinuing the Spanish abstracts. As you will see in the budget which is being presented,

the question of Latin-American membership has been deleted and this has been absorbed in the general budget since the cost for Latin-American members is not great as a result of this change.

There has also been a change with respect to the Latin-American Scholarships as the result of the paucity of residencies and training possibilities of men coming out of our own Armed Services. It has been necessary to discontinue the Latin-American Scholarships for a period of two years. As you will see, now there are only four in this country. We hope we will be able to reinstate this program, perhaps on a broader basis, when the situation clears. We are receiving requests, as are all institutions that are giving scholarships, from men from other countries, China and Spain among them. I might say that I was in Washington at the State Department meeting where I found out a number of things regarding scholarships. One of the things I was most pleased about was that probably our scholarship situation is the best of the whole bunch. The difficulties regarding scholarships are practically two; the principal one by all odds is the language difficulty. These men do not come to this country prepared to speak American. They may know idiomatic English, but when it comes to talking to patients in an outpatient department and getting a history, they are not prepared to do it. In many instances, the basic education of these men has not been up to par. Their basic education, especially in biochemistry, is not what we usually expect from our men. As a matter of fact, nearly all the men have been at least satisfactory and many of them have been outstanding, although they come from places which are especially well suited. I will come to that later.

Courses in pediatrics with which, as you know, the secretary has been concerned for the past six months have been a continual source of worry in that there are so many more applicants than positions. This matter will be brought out in a report to the Executive Board.

As you all know, much to the surprise and gratification of all of us, the amount of money asked for by the Committee on Study of Child Health Services was raised by the middle of April and that survey is going along nicely. So far as the secretary knows, there has been good cooperation by all the state chairmen and the situation bids fair to get results in the not too distant future. There are two states, namely Utah and Oklahoma, without state chairmen at the present time and until these situations are remedied, of course no surveys can be made in these states. However, I do not anticipate too much difficulty along these lines. The secretary was in Washington in April at which time he had the pleasure of visiting the headquarters for this survey. They seem ample and the staff seems to be enthusiastic and cognizant of the importance of this survey to the children of this country.

On April 13, the Secretary made a trip to Pittsburgh to the Hotel William Penn where he met Dr. Edgar E. Martner. The setup at the Hotel William Penn is as good as any we have ever had, and we should have excellent cooperation there. The local committee is cooperating in every way, and there should be a large attendance at the meeting November 13-16. We had a very satisfactory conference with Mr. Frey of the Convention Bureau of that city who volunteered to take care of hotel reservations.

Conferences on the International Congress of Pediatrics with Dr. Helmholtz and Dr. Holt proved unsatisfactory.

It is my unfortunate duty to report to you at this time the deaths of:

Dr. G. E. Harrison, Mason City, Iowa

Dr. Joseph C. G. Regan, Brooklyn, N. Y.

Dr. Chester A. Stewart, New Orleans, La.

Dr. J. Herbert Young, Newton, Mass. (Emeritus Fellow).

Respectfully submitted,

CLIFFORD G. GRULEE, Secretary

## Report of Region I

Your Regional Committee wishes to express its thanks to all the state chairmen and other fellows of the Region for their hearty cooperation in carrying out the activities of the Academy.

Since the last report the usual Academy activities have been proceeding satisfactorily in spite of the heavy load placed upon the shoulders of the state chairmen due to the Study of Child Health Services.

Dr. John P. Hubbard will present the details of the Study of Child Health Services in this region. It is gratifying to report that as of May 24 our region has a 100 per cent record for the appointment of executive secretaries to attend to the details of the Study.

Under the able leadership of Dr. Miner C. Hill, Local General Chairman, Region I held a meeting at the Pennsylvania Hotel, April 2, 3, 4. This meeting was without question the most outstanding meeting ever held in the Region. There was a registration of 884, exclusive of exhibitors. Of this number 450 Fellows were representing better than 50 per cent of our regional membership.

As for the meeting itself: The program of superlative quality was its highlight. This was prepared by our local committee consisting of Drs. Rustin McIntosh, chairman, Philip M. Stimson, cochairman, Harry Bakwin, Murray H. Bass, Adolph G. DeSanctis, L. Emmett Holt, Jr., Samuel Z. Levine, and Charles A. Weymuller.

The chairmen of the other committees were: Finance and Exhibits, Dr. Alfred E. Fisher; Publicity, Dr. Carl H. Smith; Arrangements, Dr. Thurman B. Givan; Registration, Dr. Leslie O. Ashton.

The over-all success was due to the hard work and wholehearted cooperation of these men and their assistants: The finishing touch which made the meeting complete was the work of the Women's Committee. This committee, consisting of New York pediatricians' wives, served tea, obtained theater tickets, arranged for a fashion show and other activities for the entertainment of visiting pediatricians' wives. To this committee we give our thanks.

OLIVER L. STRINGFIELD, Chairman

PAUL W. BEAVEN, Cochairman

## Report of Region II

Activity in Region II, since the last meeting of the Executive Board at Detroit in January, 1946, has been most encouraging. Much of the renewed interest in Academy affairs since World War II may be attributed to the fine objectives of the survey of Child Health Services. Pediatricians are becoming aroused to a realization of their individual responsibility and are anxious to help. The preliminary organizational work has been launched in every state of this Region, due to the excellent planning of Dr. John Hubbard the Executive Director, and his associates. More detailed information concerning progress may be obtained from Dr. Hubbard's report. It has been felt by the Regional Committee that compilation of data and direction of effort should come from the national headquarters at Bethesda; we can lend our aid in an advisory capacity in local problems which arise during the course of the survey.

Fourteen members have been elected to membership, and three names are being submitted as applicants at this meeting of the Executive Board.

A request has been received from Dr. Harvey Garrison (Mississippi) for a Regional Meeting this fall coincident with the Annual Meeting of the Southern Medical Association, and prior to the Annual Meeting of the Academy at Pittsburgh. An expression of opinion concerning this matter is desired from the Executive Board by the Regional Committee. Difficulties of planning a program upon short notice, limited clinical facilities at Miami, and the previously expressed policy of the Board against regional meetings near the date of the National Convention, present problems worthy of discussion.

State chairmen are, in most instances, participating very actively in the survey. No formal reports have been requested from them concerning their general Academy responsibilities on account of the current detailed demands of this work.

Respectfully Submitted,

WARREN W. QUILIAN, Chairman Region II

JAMES W. BRUCE, Associate Chairman Region II

### Report of Region III

Five new state chairmen have been appointed in Region III. They are:

Dr. Benjamin Hoyer, Ohio  
Dr. Ernest Carlo, Indiana  
Dr. Henry Poncher, Illinois  
Dr. James E. Dyson, Iowa  
Dr. Roland E. Nutting, Minnesota

Reports from the state chairmen of Region III indicate that most of their activities during this year have been concerned with the Child Health Survey. This work will be reported in detail by Dr. Hubbard.

Dr. Poncher reports from Illinois that the Academy is active in the State Rheumatic Fever program and in the Parent Teacher Association plans for summer round-up examinations is in contact with the Mayor's committee concerning preschool health programs in Chicago and is interested in establishing an extension of health services by setting up several downstate health centers in communities where such medical attention has not been available to mothers and children.

In several other states, child welfare work is going on in cooperation with the American Legion. Activity is also reported in school health problems and in infant health problems. In general, usual Academy activities in the region have been held somewhat in abeyance so that proper attention may be given to the Child Health Survey which is now under way in most of the states of the region. There was no report from five of the states.

The financial statement for the region remains unchanged since the January report. Total assets remain at \$4,061.68, except for uncomputed accumulated interest since January, 1946, on deposits of \$2,211.65.

In addition to these funds, the treasurer of the Academy holds bonds to the credit of Region III in the amount of \$1,850.00 with a face value of \$2,500.00.

Present enrollment in Region III is four hundred and eighty members. Twenty-two applicants will be voted on at the June meeting of the Executive Board.

Respectfully,

GEORGE F. MUNNS, Regional Chairman

### Report of Region IV

The past year, from the pediatric point of view, has varied but little from the war years. The stress of work for those not privileged to be in the Armed Forces for the most part has prohibited all medical activities other than the daily grind of private practice.

Last year we expressed the hope that the return of many of the men from the Military Services would so ease matters that Academy activities might again be resumed. This hope has not been realized. Although many men have returned, they have been so occupied with such minor diversions as finding a place to live and finding office space, that they have furnished little relief and have had little time to spare over and above the time spent on these things. Last fall the membership expressed the desire to hold a regional meeting this spring and much effort was expended in trying to locate a satisfactory place for such a meeting, to no avail. At this time it does seem possible that the annual meetings may be resumed in the spring of 1947.

The Southwest Pediatric Society, most of whose members are also members of the Academy, expects to resume its three-day session and lecture course in September of this year.

Perhaps the most important news items from the west coast and Region IV are (1) the decision by the University of California to establish a new medical school in Los Angeles; funds for this project have been appropriated, and the next year should see it well under way and (2) entrance of the first class into the University of Washington Medical School in the fall of 1946.

Respectfully submitted,

HUGH K. BENKLEY, Chairman Region IV

VERNON W. SPICKARD, Associate Chairman Region IV

## Report of Region V

The matter of most importance for consideration by this Executive Board concerning Region V is the one related to the decision in reference to the celebration of the First Pan-American Congress of Pediatrics and the definite possibilities of its coming through.

I have amply informed all the Latin-American groups of the decision reached by this Academy. In principle, which is to be expected, there is great satisfaction and interest in this Congress. But especially Drs. Garrahan of Buenos Aires, Krumdieck of Lima, and Gomez of Mexico, pointed out the previous agreement, which was reached in Chile, to celebrate a Latin-American Pediatric Reunion in the fall of 1948. They consider, therefore, that the reunion planned by the Academy may interfere with the one in Buenos Aires.

Since our decision, the organizing committee of the International Congress of Pediatrics insisted on celebrating their reunion in the fall of 1947, presenting various reasons in accordance with the colleagues of Europe and the representatives of the American Pediatric Society and the Society for Pediatric Research.

Accepting Dr. Helmholtz' kind invitation, we have had the opportunity to exchange our points of view on this particular matter at Sky Top, Pa., discussing carefully the pros and cons as to these reunions and the possibilities of extending our cooperation to the same.

To that effect we have had an urgent consultation with the Latin-American centers, especially those of greatest pediatric activity, such as Argentine, Mexico, Chile, and Brazil; and the consensus of opinion is in favor of an intelligent coordination of the different pediatric events.

It is convenient to inform this Executive Board of some of the aspects of pediatrics in Latin America.

There are in Latin America many pediatric societies perfectly organized, whose contribution in the field of scientific research is quite outstanding.

Argentina has the "Society of Pediatrics of Buenos Aires, del Rosario and of Cordoba," with more than 200 members. Only 21 pediatricians belong to the American branch.

Chile has "La Sociedad Chilena de Pediatria" in Santiago and "La Sociedad de Pediatria de Valparaiso" with about 153 members. Only 13 belong to the branch of the American Academy.

Mexico has "La Sociedad Mexicana de Pediatria" with more than 100 members, 15 belonging to the American branch.

Brazil has "Las Sociedades de Pediatria de Rio de Janeiro y San Pablo" with more than 100 members, 25 belonging to the American Academy.

Colombia has 50 members, of which 7 belongs to the American Academy.

Peru has more than 60 members of which 7 belong to the American Academy.

Uruguay has "La Sociedad Uruguay de Pediatria" with more than 100 members, 28 belonging to the American Academy.

Cuba has more than 150 members of which 13 belong to the American Academy.

Thus we can see that the number of members belonging to organized societies of pediatrics reaches above 1,000 in Latin America, of which only 163 are members of the American Academy of Pediatrics, which represents only 16 per cent.

The International Congress is a permanent institution with periodical reunions of international official character and the invitations to attend these are transmitted through official channels through the Department of State.

When the different governments of Latin America receive the invitations through their respective legations and embassies they will proceed immediately to designate their corresponding delegates, it being our mission to see to it that these designations fall upon members of the American Academy of Pediatrics since these are the most influential and distinguished in each country.

Far from being a handicap, the celebration of the International Congress is a motive favorable to the reunion of the members of Region V, Latin-American Division.

Because of all this we feel that it is to the interest of Region V that the Academy offer its cooperation to the celebration of the International Congress, designating to this effect three of its members to become members of the Executive Committee of the International Congress, in conjunction with the members belonging to the American Pediatric Society, the Society for Pediatric Research, and the Pediatric Section of the American Medical Association which, together with the officials designated in Rome, should constitute the Grand Organizing Committee.

We believe that it is fitting that one of the three members of the American Academy should be the Chairman of Region V, in that he represents the incorporation of twenty countries.

The Latin-American pediatricians will present to the Committee of the International Congress their points of view, which refer principally to the motion of declaring Spanish as an official language and to the active participation of the Latin pediatricians as official participators in the Congress.

In conclusion, Region V presents to the Executive Board of this Academy, the following motions:

1. The Executive Board backs the celebration of the International Congress of Pediatrics to be held in the city of New York in the fall of 1947.
2. Authorize the President to designate three members of this Executive Board who will become members of the Executive Board of the International Congress.
3. Authorize the Chairman of Region V to convoke the members of this region three days previously to the International Congress at which time the meeting of Region V will be organized in order to develop the planned program by the Organizing Committee of the First Pan-American Congress of Pediatrics.

In the name of the Latin Pediatricians that constitute Region V, I beg the members of this Executive Committee to back this motion that tends to coordinate the different events planned, facilitating in this manner the celebration of the International Congress of Pediatrics in the fall of 1947, the celebration at the same time of the general meeting of Region V, and at such time permit us to extend our cooperation to the fullest success of the reunion in Buenos Aires in 1948.

Respectfully submitted,

FÉLIX HURTADO, Chairman, Region V

### Report of the Treasurer

Dues for 1946-1947 were placed at \$25.00 including \$5.00 for subscription to the JOURNAL. The \$5.00 dues for Region V were discussed and all members were put on a \$10.00 a year basis.

It was voted that a charge of \$2.00 be made for each round table at the annual meeting.

### Report of the Treasurer

#### STATEMENT OF RECEIPTS AND DISBURSEMENTS, JULY 1, 1945, TO MAY 31, 1946

Balance in checking account, July 1, 1945	\$ 344.33
Balance in savings account, State Bank & Trust Company	3,838.72
Balance in savings account, First National Bank & Trust Co.	1,544.61
	<u>\$ 5,727.66</u>



*Receipts:*

Dues		\$28,323.61	
Wartime assessment		6,795.00	
Exhibits—January, 1946 Meeting		8,230.00	
Initiation fees		3,925.00	
Interest earned		944.62	
Pamphlets—Child Health Record	\$ 399.31		
Immunization Procedures	424.55		
Vitamins	18.80	842.66	
Subscriptions—Men in Service		897.50	
Committee—Post-War Courses		10,000.00	
Bonds sold		10,000.00	69,958.39
			<u>\$75,686.05</u>

*Disbursements:*

Annual Meeting—January, 1946		3,984.97	
Annual Meeting—November, 1946		59.48	
Bank charge and exchange		129.23	
Certificates and mounting		74.03	
Executive Board		2,598.64	
Miscellaneous		297.57	
Office supplies and equipment		221.84	
Postage		565.57	
Rent		2,557.36	
Salaries—Secretary	\$8,750.00		
Assistant Secretary	1,283.32		
Stenographer	2,390.00		
Office	1,428.71	13,852.03	
Stationery and printing		1,661.07	
Subscriptions		7,962.07	
Telephone and telegrams		480.36	
Travel—Secretary		434.08	
Treasurers' bonds		85.00	
Expense—Region I	\$ 39.26		
Region III	5.50		
Region V	1,959.68	2,004.44	
Expense—States (Region I)	50.53		
(Region II)	30.26		
(Region III)	18.09	98.88	
Expense—Committees			
Cooperation With American Legion	395.21		
Legislation	25.00		
Post-War Courses	\$1,345.33		
Post-War Planning	17,348.52		
Rheumatic Fever	100.00		
Special	22.05	19,236.11	
Pamphlets—Child Health Record	26.66		
Immunization Procedures	27.54		
Vitamins	7.8	54.98	56,357.71
			<u>\$19,328.34</u>
Balance in checking account, May 31, 1946			\$ 9,993.45
Balance in savings account, State Bank & Trust Company			7,782.56
Balance in savings account, First National Bank & Trust Co.			1,552.33
			<u>\$19,328.34</u>

## Reports of Committees

### Report of the Committee for the Study of Child Health Services\*

The executive Staff for the Study of Child Health Services has greatly increased in number since its early beginning. Dr. Montgomery Blair, Jr., was appointed as Assistant to the Director in February, 1946. Dr. John M. Mitchell has recently been added to the executive staff. Regional directors who have been appointed without necessarily adhering to existing regional divisions of the Academy are as follows: Dr. Lendon Snedeker for the New England States, Dr. Ward L. Chadwick for the Midwestern States between the Mississippi and the Rocky Mountains, and Dr. H. E. Thelander for the Far West. Including these Regional Directors the personnel of the Central Office totals twenty-two, of whom ten are on the payroll of the Academy, three on the payroll of the Children's Bureau and nine on the payroll of the United States Public Health Service.

In order to finance the Study, additional funds have been received. In accordance with action taken by the Executive Board of the Academy at the annual meeting in Detroit in January, 1946, \$10,000 has been received from the reserve fund in addition to the \$8,000 originally appropriated. Grants have been received or pledged on a two-year basis from the following Foundations which had previously been approached: National Foundation for Infantile Paralysis, Inc., \$116,000, Field Foundation, \$10,000. Since January, 1946, a total of \$85,000 has been received or pledged from the following pharmaceutical houses: Mead Johnson and Company, Lederle Laboratories, Inc., M & R Dietetic Laboratories, Inc., Pet Milk Company, and Carnation Company. (Mead Johnson and Company had previously given \$8,000).

In accordance with the budget originally submitted, these funds are to cover the salaries of the Executive Staff and the operating expenses of the Central Office. In addition to these funds, state programs are being financed from within their own borders with the support of funds available through county chapters of the National Foundation for Infantile Paralysis, State health departments, State foundations and pharmaceutical houses, contributions from medical and pediatric societies and from individual pediatricians. When State programs have been fully developed and financed from sources at State level, the responsibility of the Academy as expressed in the over-all budget will have been fulfilled.

The organization of state programs has progressed rapidly throughout the country. Obviously those state chairman who have been able to secure the services of full-time executive secretaries have been able to make the greatest advances. The rapidity with which state programs have been developed and the extent to which difficulties have been met by state chairmen and executive secretaries represents an outstanding achievement. As of June 1, 1946, executive secretaries have been appointed in 38 states. In these states the programs are well under way and the distribution and collection of schedules has begun. Approval of the Study by pediatric groups has been reported from 34 states. Endorsement of the project has been received from 37 state medical societies and 42 State departments of health. A total of 45 states and the District of Columbia are now in the process of organizing their programs. Up to June 1, only 3 states have failed to report active organization and approval of state study programs.

Plans are now being developed for tabulation of data. These plans are based largely on the experience obtained from the pilot study in North Carolina. A major phase deals with the question of classification of the material to bring out differences in the distribution of health and medical services for children. Tables and maps grouping hospital, physician, and dental services in several states, according to various characteristics of counties, were presented in April to some of the members of the Committee for the Study of Child Health Services and on May 24, 1946, to the Advisory Committee. The items considered for each county were: metropolitan character, size of largest city, and purchasing power. This approach has led to a definite plan for showing the distribution of health and medical services for children in various parts of each state to bring out disparities which may exist. Coding

\*The report of the Committee for Study of Child Health Services was delivered in person by Dr. John P. Hubbard and Mrs. Elizabeth Lammie.

and tabulating of the information received will be carried out in the Central Office for analyses on a national level to make available to state pediatric groups basic data on facilities and services. This work has already been started and will continue as rapidly as the data are received from the states.

Respectfully submitted.

WARREN R. SISSON, Chairman  
JOHN P. HUBBARD, Director  
ALLAN M. BUTLER  
HARVEY F. GARRISON  
LEE FORREST HILL

JOSEPH I. LINDE  
ARTHUR H. LONDON, JR.  
JOSEPH S. WALL  
JAMES L. WILSON

This report was accepted.

Mr. A. L. Rose of Mead Johnson and Company reported on the film, "When Bobby Goes to School" and asked that some revisions be made. This was referred to the Committee on Cooperation with Nonmedical Groups. He also reported on a small fund which is accumulating there, which he is going to place at the disposal of the Academy. He next offered a contribution for the development of a museum and library. This was referred to the Committee on a Library and Museum of Pediatrics for a conference and recommendations.

The term of office for Region V of Drs. Félix Hurtado, Víctor Escardó y Anaya, and Federico Gómez Santos was continued until the next meeting of the Academy at Pittsburgh.

#### Report of the Committee on Redistricting

With the addition of the new members elected today, the total number in each district will be as follows:

District 1	203	District 6	240
District 2	210	District 7	250
District 3	244	District 8	227
District 4	211	District 9	161 approximately
District 5	245		

It was decided that for the present we would pay for publicity by the meeting instead of by the year.

After discussion of scientific exhibits and their method of assignment the whole matter was left in the hands of the Secretary.

Respectfully submitted,

EDGAR E. MARTNER, Chairman

This report was accepted.

#### Report of the Committee on Cooperation With Nonmedical Groups

The Committee on Cooperation with Nonmedical Groups discussed a program at the annual meeting in Detroit. Contact is being made with a number of lay groups interested in children, offering medical assistance in their programs. The health card designed for camp use has had wide distribution. Several changes have been suggested to improve the card. These changes will be made at the next printing. No concrete program has been outlined for this year.

ALBERT D. KAISER, Chairman

This report was accepted.

#### Report of the Committee on Cooperation With Governmental and Medical Agencies

Due to the national situation concerning child health legislation, no formal meeting of this committee has been held since May, 1945, to give the Academy opportunity to clarify its policy with regard to the national situation. Two informal meetings, of such members of the Committee as were able to be present, were held in Detroit and New York to discuss future activities. In Detroit, the tentative decision of those present was that the committee should (1) reactivate the state programs in our forty-eight states and reconstitute able state committees, (2) to act as advisers to the Bureau of Food and Drugs of the Federal Security

Administration through a special subcommittee headed by Dr. Harold Murray of Newark, and (3) to promote our Academy-accepted national program in every possible way as an aid to the composition of the national child health situation.

At the New York meeting, Dr. Van Horn kindly offered to provide data as to state councils for children and youth, which have been formed in many states, and this information will be made available to our state committees as soon as they are reconstituted. In the meantime, the Academy state chairmen will receive this material.

A regular meeting of the Committee will be held in Pittsburgh at the time of the annual meeting of the Academy in November, 1946.

With the able assistance of Drs. Joseph Wall, Martha Elliot, A. Leonard Van Horn, Thomas Parrau, R. C. Williams, Erval Coffey, Roger Lee, Louis Bauer, and Oliver Stringfield, the Committee sponsored a panel discussion at the regional meeting in New York on "Cooperative National Planning for Improving Child Health Services," which was very well received. It is hoped that a digest of this panel will be printed in the *JOURNAL* for the information of the Fellows.

In view of the fact that there has been no formal meeting of the Committee, the Chairman is enclosing his introductory statement at the panel discussion, which he requests be made part of this report as it covers the Committee's past progress and plans for the coming year, for the consideration of the Academy and the Executive Board. The United Nations Constitution states its purpose as follows: "To preserve peace and to promote social progress and better standards of life in larger freedom." This might well be the motto of our committee, and with our membership strengthened by the recent addition of those two able pediatric statesmen, Drs. Wilburt Davison and Joseph Wall, we shall do our best this year to promote cooperation between governmental and medical agencies at both State and National levels.

Respectfully submitted,

STANLEY NICHOLS, Chairman

This report was accepted.

### Report of the Committee on School Health

Your Committee recommends the publication of the enclosed Resolution of the Association of State and Territorial Health Officers. In the opinion of your committee this resolution is a reasonable proposal to meet "the present impasse in the jurisdiction of school health between boards of education and departments of health" as mentioned in the Report of the Committee on a Consideration of Child Health in the Postwar Period (*J. PEDIAT.* 25: 625, 1944).

During the past year your chairman has served on several committees of the National Conference on Cooperation in Health Education. "Suggested School Health Policies," second edition, has recently been published after revision by the National Committee on School Health Policies of the National Conference for Cooperation in Health Education. Three Federal agencies and twelve national professional organizations nominated representatives to this committee including the Academy. Also Dr. Wheatley, of your committee, was nominated by the U. S. Children's Bureau. The report indicates the scope of the school health program and suggests policies acceptable to the representatives of the various educational, medical, dental, and public health associations. The report is significant as a type of interprofessional cooperation and is particularly recommended as a basis for the development of local and state policies. While different emphases in the report may be desired by one professional group or another, the two Academy members on this national committee recommend the report because it provides a common ground of opinion and a guide for much needed improvement that must be worked out on the local level. While such a cooperative report represents some compromise, the differences of the Academy representatives were wholly upon emphasis, and not upon principles.

The revision of the joint report, "Rheumatic Fever and the School Child," has not been completed and will be forwarded later.

Your Committee has given consideration to S. J. Res. 137, introduced by Senator Morse on January 29. This resolution authorizes the Department of Labor, acting through the Children's Bureau, to make certain studies of the health of school children. While this resolution neglects the important problem of Federal organization and jurisdiction in the distribution of funds, it should serve to encourage much needed fact-finding studies and demonstration of methods as a compromise measure. To this extent it is consistent with the position of the Academy. Dr. Martha Eliot writes concerning this resolution that the cooperation of the U. S. Public Health Service and the U. S. Office of Education would be sought in planning projects and considering relationships with the Academy study. We recommend that on Line 9 of the resolution a change be inserted after the word "*schools*"—the words—"*and health departments*" and in the same line—after the word "*physical*" there should be inserted "*and other handicapping.*"

*The Committee on School Health Proposes a Broader Objective for School Medical Service To Improve School Medical Service*

The question, how we can improve the quality of medical service in school health programs, has long been of particular interest to the Academy. The problem involves not merely more thorough health examinations, but a better understanding and closer liaison between the school health authorities and the practicing physician who cares for the child outside of school.

This can be best achieved through the leadership of the medical profession who are concerned with medical education. The physician serving school age children should have postgraduate education in this branch of pediatrics. This training should include, in addition, emphasis on techniques of personal health guidance to enable the physician more effectively to persuade and educate parents and teachers in the health care and education of children.

To embrace as large a proportion as possible of the medical profession in such a medical education program, and to engage the best qualified medical educators to participate in this medical educational program, health authorities should provide:

1. Part-time employment of school physicians for limited periods.
2. High standard in-service training courses with competent clinical instruction.
3. Reasonably generous remuneration\* to the part-time physicians and to the teachers of the in-service training courses.

*Physicians as Health Educators*

There is a growing recognition of the importance of community programs for health education and yet there is little evidence of an appreciation of the possibilities of making use of the contribution that might be made by the medical profession. The doctor, who calls on the sick in the home, who advises and prescribes in his office, who serves in the hospital or clinic, has such opportunities for effective health knowledge if these occasions were used by physicians. Better health education by physicians can be achieved only through the channel of postgraduate medical education.

*Pediatricians Teach Parents*

The competent pediatrician who is able to maintain the kind of practice that brings well children to his office for advice and supervision certainly illustrates effective health teaching that represents the highest quality of public service. To extend this high standard of preventive medical practice, so that more physicians may give such health education for mothers and children, should be a more clearly defined objective of the public health program. It is then one of the needs that is desirable for the public welfare that more physicians should have an opportunity to learn how to give this high standard of preventive pediatrics and at the same time educate parents to understand that health advice is worth while.

\*Such service should be paid at a rate for each hour of service at least equal to the average for an office visit to a qualified pediatrician.

*Medical Education as Health Department Policy*

While the American Academy of Pediatrics, the American Medical Association, and the American Public Health Association have all urged more postgraduate education of physicians as a fundamental requirement for a national health program, there has never been any well-defined policy or general acceptance by health departments or other governmental agencies below the Federal level of postgraduate medical education as an essential part of the public health program, except as has been necessary for the benefit of the treatment of venereal disease and occasional lectures to medical societies. We regard this as a serious neglect of an essential part of the public health program.

*Child Health Services Offer Opportunity*

We believe that school medical service and child care offers an opportunity for training of physicians in preventive pediatrics and health education of parents that is a fundamental requirement for the extension of improved medical service and health education. Such an objective of the public health program cannot be achieved through any known methods for teaching in an already overcrowded undergraduate medical curriculum.

Postgraduate opportunities in preventive pediatrics could reach many more medical practitioners if part-time school and child health conference positions in health departments were on limited tenure and provided postgraduate teaching on a par with the teaching in medical schools and many pediatric clinics. These services also should pay sufficient remuneration so that young well-trained physicians would be able to accept the service without financial sacrifice.

With competent teaching, the services would soon become very desirable and over a period of years would provide preventive pediatrics training to a large part of the profession serving children. Such a contribution to better medical service would be of great benefit to the public and would undoubtedly bring a better understanding of these public services to practicing physicians.

*Public Funds to Benefit All the People*

The limited efforts of the Federal services to train public health officials and other specialists to contribute to child health, while useful, have been altogether inadequate and never can meet the need for maintaining high quality of service throughout the country without a full acceptance of the responsibility for the administration at the local level.

This means that local health departments must use local funds for postgraduate medical education or funds from a Federal or State source with local planning and administration to improve the quality of medical service and not limit the medical educational opportunities to build up public health services without regard for the medical services rendered outside of the health department services. Public funds for improving the quality of medical service should benefit all of the people and the extension of postgraduate medical educational opportunities is essential for the improvement of preventive medicine for the whole population.

*Health Department Physicians Learn Preventive Medicine*

Fortunately the Health Department program generally calls for a development of preventive medical services by physicians giving part-time service to individuals so that teaching preventive medicine to part-time Health Department physicians can contribute to the larger objective of more and better preventive medicine for all the people. With limited tenure for the Health Department physicians the medical education program for preventive service can be extended to a large part of the profession and in turn benefit all the people served by the profession.

*More Funds for Health Departments to Fulfill Their Mission*

Of course, with Health Departments very short on funds for their services, there is a tendency to conserve those funds and to rely on administrative procedures rather than medical

education to improve the services, and yet with a growing realization of the necessity for more medical education to improve the quality of service, we should demand that public health services today fulfill their mission just as William Osler said at the turn of the century that "No hospital could fulfill its mission that was not a centre for the instruction of students and doctors."\* We should then set as our objective a broad acceptance of the principle that Health Departments should employ part-time physicians on limited tenure with adequate remuneration, and the Academy should use these facilities to extend opportunities to general practitioners and young physicians to give better preventive services to children and to educate parents on the care of children's health.

### *The Example of the Veteran's Administration*

It seems likely that the restrictions and rules and regulations of Civil Service Commissions will prove a handicap to such a program for medical teaching in Health Department Child Health Services, but we have an excellent recognition of this problem by the United States Veteran's Administration and the new law, signed by President Truman on January 3, creating a Veteran's Administration Bureau of Medicine and Surgery. This law authorizes the new Bureau to employ physicians outside of the normal requirements of civil service, and it has been brought out in the discussions of that legislation that the civil service requirements interfered with obtaining the most competent physicians.

### *Academy Leadership*

The development of this proposal will require active leadership from the Academy and some plan for the development of a staff for teaching and for appointing the young physicians, according to the standards recommended by this Committee in 1942 and published in the *Journal of Pediatrics* in December, 1942, and also by the *American Journal of Public Health*.

### *A Plan for Teaching Physicians*

This in-service course should provide for the pediatric teaching staff to observe the young physician in the Child Health services and for discussion of findings and recommendations and education of parents, seminars on growth and development, and round table discussion of common medical problems of children—such as nose and throat conditions, allergy, nutrition, endocrinology, rheumatic fever, and mental health.

Consultation services should be available and provision should be made for the physician in the schools to consult with a competent cardiologist, otologist, orthopedist, dentist, psychiatrist, dermatologist, and ophthalmologist on cases selected for referral to these services. The major portion of the teaching should be carried by the pediatrician but such consultation services should be available when indicated so that the highest standards of medical judgment may be maintained. Seminars with such consultants should be included to develop further information on the use of specialists in the care and supervision of children.

The report of the Committee on School Health was accepted.

Dr. Mitchell was invited to appear before the Executive Board at its next meeting to further elucidate the various phases of his committee report.

### **Report of the Committee on Hospitals and Dispensaries**

We are at the present time taking up the question of standards for pediatric clinics. I have been in touch with the members of my committee but as yet there has not been sufficient time to collect material for this report.

Respectfully submitted,  
JOHN A. BIGLER, Chairman.

This report was accepted.

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\*Cushing, Harvey: *The Life of Sir William Osler*, Vol. I, p. 540.

## Report of Committee on Legislation

Gentlemen:

I regret very much my inability to attend your meeting through the kind invitation of President Durand and Secretary Grulee, but, unfortunately, hearings on the Pepper-Norton bill have been initiated on the House side of the Congress and I have been asked to appear before the House Sub Committee on Labor, Representative Augustine B. Kelley, chairman, on June 7, which date would coincide with the meeting of your Board in Chicago.

The following report, which must be regarded as that of the chairman of the legislative committee only, as we have had no meetings of the new committee appointed by President Durand nor any conferences by correspondence as yet, includes the steps taken by your chairman to present properly the opinions of the Academy on legislation in the process of hearings before the Senate Committee on Education and Labor and the House Committee similarly named, now considering the Pepper bill since May 28.

We were particularly anxious to have officers of the Academy appear before the Senate Committee in re S. 1606, the Wagner-Murray-Dingell bill, as Title I, Part B of this bill is a compressed version of the Pepper bill, and Senator Pepper has already proposed amendments which he will seek to have inserted in S. 1606 to make it comparable more closely to S. 1318 which he introduced.

Learning in March that hearings on the Wagner bill would start in April, I addressed the following communication to Senator James E. Murray, Chairman of the Senate Committee on Education and Labor, under date of March 10, 1946:

Senator James E. Murray, Chairman, etc.

Dear Senator Murray:

I would respectfully ask permission to appear before your committee during the hearings on S. 1606 and also when S. 1318 will be under consideration.

This request is made because of my official connection with the American Academy of Pediatrics, as chairman of its Committee on Legislation and with the Medical Society of the District of Columbia, as chairman of its Committee on Public Policy.

Sincerely yours,

JOSEPH S. WALL, M.D.

On March 25, I received a telegram from Senator Murray asking that I submit a written statement instead of appearing in person, as the time of the committee was limited, etc., etc.

The next day, on March 26, I addressed the following letter to Senator Murray:

Hon. James E. Murray, etc., etc.

My dear Senator:

I was much surprised to receive your telegram requesting that the views of the American Academy of Pediatrics on the National Health Act be reduced to writing in substitution for an oral presentation before the Senate Committee on Education and Labor.

I had been given to understand that *national* organizations would be heard in opposition and for some ten years, as Chairman of the Committee on Legislation, it has been my duty to represent the American Academy of Pediatrics in legislative or departmental matters.

I trust that not only may my request be reconsidered, but that the President-Elect of the Academy, Dr. Lee Forrest Hill of 604 Locust St., Des Moines 9, Iowa, and the Assistant Secretary, Dr. Edgar E. Martmer of 693 Washington Road, Grosse Pointe, Michigan, be requested to appear personally before your committee.

The American Academy of Pediatrics has a state-wide membership of nearly two thousand pediatricians who have an intimate interest in S. 1606, especially Title I, Part B, as well as in its general purposes.

Sincerely yours,

JOSEPH S. WALL, M.D., etc.



On March 29, the following telegram was received from Senator Murray:

Dr. Joseph S. Wall, etc., etc. Relet March 26 I understand and appreciate your interest in testifying personally on the National Health Bill. I deeply regret that during the hearings thus far scheduled there has been no opportunity allocate time for representatives of special aspects of medical science. However, the committee may decide to extend the hearings to hear witnesses such as yourself and I have appointed a special subcommittee to handle this question. Let me assure you that your request will be sympathetically considered by this subcommittee. In the meantime would appreciate it if you could send a written statement.

(signed) JAMES E. MURRAY, Chairman, etc., etc.

After some days, I learned that Senator H. Alexander Smith of New Jersey (with whom Dr. Stanley Nichols had enjoyed some contact already) would be made chairman of the subcommittee referred to by Senator Murray. Under date of April 15 the following letter was addressed to Senator Smith:

Hon. H. Alexander Smith  
Committee on Education and Labor, U. S. Senate.  
My dear Senator:

As Chairman of the Committee on Legislation of the American Academy of Pediatrics, I requested twice of Senator James E. Murray the opportunity of appearing before his committee in opposition to the Wagner-Murray-Dingell bill but was not accorded this request.

I would respectfully ask the privilege of appearing before the subcommittee as a representative of the organization named which is much interested in the welfare of children and in matters of legislation affecting their interests.

Sincerely yours, etc., etc.

On April 29, Senator Murray telegraphed me as follows:

Dr. Joseph S. Wall, Am. Academy of Pediatrics, 1864 Wyo. Ave.

Shall greatly appreciate your making arrangements for a representative of your organization to present testimony on National Health Bill before Education and Labor Committee on morning of Wednesday May 29. Please confirm with name and title of person who will speak for you.

JAMES E. MURRAY, etc.

In reply to this telegram, the following letter was sent:

Hon. James E. Murray, etc., etc.

I appreciate the opportunity of appearing before your committee on May 29, to testify on behalf of the American Academy of Pediatrics in opposition to the National Health Act as at present written.

As I have indicated in previous letters requesting this privilege as Chairman of the Committee on Legislation of the Academy, I would also request that there be permitted to appear the President-Elect, Dr. Lee Forrest Hill of 604 Locust St., Des Moines 9, Iowa, and the Assistant Secretary, Dr. Edgar E. Martmer of 693 Washington Road, Grosse Pointe, Michigan.

Very sincerely,

JOSEPH S. WALL, M.D., etc.

May 4, 1946.

No invitation was extended to Dr. Hill until such a late date that his appearance in person was out of the question. I have had no word from Assistant Secretary Martmer as to whether or not he received an invitation to appear from the Senate Committee.

This morning, May 31, I appeared before the Senate Committee on Education and Labor and presented a written statement which now follows, and which I trust reflects the views of the Academy on the legislation under consideration, the Wagner-Murray-Dingell bill. There were present at the hearing only Senators Murray and Donnell (of Missouri), the latter being strongly opposed to the bill. Senator Donnell, at the conclusion of the presentation, thanked me on the part of the Committee for my appearance and asked that I especially convey his appreciation to the Academy of Pediatrics itself.

The statement follows:

The objections of the Academy of Pediatrics to the enactment of S. 1606 are based upon the general principles that such would be deleterious to the interests of the children of the country, aside from its harmful effects upon the science of pediatrics and the education of pediatricians.

In justification for requesting the privilege of appearance before this Committee in opposition to the enactment of the National Health Act as at present written, we would submit the following information concerning the composition, activities and purposes of the American Academy of Pediatrics.

The Academy is a national organization of nearly 2,000 children's specialists. It is in reality an international and hemispherical organization inasmuch as its membership includes children's physicians in Canada, Mexico, Cuba, Puerto Rico, and all of the republics of South and Central America save one.

The purposes of the Academy of Pediatrics are set forth as follows in its constitution:

Article III, Section 1: The object of the Academy shall be to foster and stimulate interest in pediatrics and correlate all aspects of the work for the welfare of children which properly come within the scope of pediatrics.

The Academy shall endeavor to accomplish the following purposes:

- (a) To establish and maintain the highest possible standards for pediatric education in medical schools and hospitals, pediatric practice and research;
- (b) To perpetuate the history and best traditions of pediatric practice and ethics;
- (c) To maintain the dignity and efficiency of pediatric practice.
- (d) To promote publications and encourage contributions to medical and scientific literature pertaining to pediatrics; none of which objects is for pecuniary profit.

Furthermore, the Academy has demonstrated its active interest in the welfare of the children of the Nation by inaugurating last year a "study of child health services" throughout every State, county and city in our country. This study is now in actual progress under the direction of able administrators and investigators, and contemplates a work of two years' duration at a cost of approximately a half million dollars. The funds for this state-wide investigation of the needs of children have been provided from the limited reserves of the Academy itself and from other organizations interested in the welfare of children, including a grant-in-aid of 116 thousand dollars by the National Foundation for Infantile Paralysis. This study also has the assistance and cooperation of the U. S. Public Health Service and of the Children's Bureau of the U. S. Department of Labor.

The aims of the Academy and of its individual members are encompassed in the first paragraph of this study committee's report, namely: "To make available to all mothers and children in the United States of America all essential preventive, diagnostic and curative medical services of high quality, which, used in cooperation with the other services for children, will make this country an ideal place for children to grow into responsible citizens."

Our objectives and aspirations coincide exactly with those of the more vocal, social, and political reformers, utopian evangelists, and some fanatical crusaders

whose enthusiasm too often outruns the boundaries of common sense and realism. We, too, seek diligently the Holy Grail symbolic of perfection in mother and child protection from the vicissitudes of ill-health. Our quest differs not from that of the social crusaders, our goals and desires are equally alike, but the methods of attaining these ends, from our point of view, do not agree in many respects with the programs thrust upon us, usually without our knowledge and without the utilization of that experience we possess in the practice of pediatrics which should be recognized as necessary in determining the success or failure of any projected planning for child betterment.

The Academy approves of the objectives of Title I, Part A relating to grants to States for Public Health Services, but feels that greater effort should be made in health legislation to care for general measures of sanitation relating to factors bearing upon health such as water supply, food and milk supply, sewage disposal and the like. Nor can the Academy approve of the actual prohibitions contained in the National Health Act as outlined on page 13, lines 12 to 17 inclusive, to wit:

"The term does not include: construction of hospitals, water supplies, sewerage or other waste-disposal systems, or of other facilities; operation or maintenance of hospitals (except hospitals for persons afflicted with infectious diseases), water supplies, sewerage or other waste-disposal systems; and related matters."

Title I, Part B, is in reality an abbreviated version of S. 1318 (the Pepper bill), dealing with grants-in-aid to States for maternal and child health services, including the care of crippled children, although much of the detail of S. 1318 has been omitted.

The Academy sees no necessity for and objects to the blanket coverage for "all mothers and children in the State or locality who elect to participate in the program." (Page 16, lines 2, 3, and 4.)

Present organic law, the Social Security Act, as amended, provides for support from the Federal government to States, "especially in rural areas and in areas suffering from economic distress," under Title V, parts 1, 2, and 3, covering practically the identical needs of children now set forth in Title I, Part B, of the National Health Act of 1946, the coverage being limited because of the specification of funds to be allotted for these purposes.

The Academy has always urged that the Congress grant adequate appropriations to carry out such programs for maternal and child health and crippled children's services for needy persons. Representations have recently been made on the part of the Academy to the Ways and Means Committee of the House to remove the financial restrictions now specified under Title V of the Social Security Act, in order that more adequate funds shall be made available to the Children's Bureau to extend provisions of its present progress.

The absence of a "means test" with the opening of the doors in Title I, Part B, to "all mothers and children in the State or locality who elect to participate in the program" (page 16, line 8), together with the provisions of Title II, Section 201 (a), that—"Every individual, who is currently insured, and has been determined by the Board to be eligible for benefits under this title in a current benefit year, shall be entitled to receive personal health benefits," constitute serious objections, in the opinion of the Academy, to the adoption of such legislation.

An Act conceived to provide adequate medical care for those in low economic groups, which actually discriminates against these individuals by diminishing funds available for their medical care due to the inclusion of all persons, regardless of income or financial status, is certainly of questionable justice or equity.

We object to the provisions of Title I, Part B, and of Title II, because of the omission of an adequate and equitable means test in determining eligibility for benefits under the program. On the other hand, the Academy of Pediatrics favors the expenditure of Federal and State moneys for the benefit of those in need and unable to provide proper medical care for their own resources.

Strange as it may seem, the proposed National Health Act *does* incorporate in its paragraphs several means tests, one of which is implied and others directly named, one of the latter having application both to "the quick and the dead."

The first means test of sorts is that which specifies a ceiling to taxable wages up to \$3,600 a year, although not mentioning a floor, but which thereby excludes all but the wage earner (or self-insured, page 76, lines 14, 15, and 16) from personal health benefits under this section. This exclusion from personal health benefits of persons who have no "means," who are furthermore, the very individuals whose need the Act is intended to relieve from a humanitarian standpoint, is supposed to be rectified by Section 209 (a) of Title II, which reads as follows:

"Notwithstanding any other provision of this title, any or all benefits provided under this title to individuals entitled to such benefits may be furnished to other individuals for any period for which equitable reimbursements to the Account on behalf of such other individuals have been made or for which reasonable assurance of such reimbursements has been given by public agencies of the United States, the several States, or any of them or of their political subdivisions, such reimbursements to be made in accordance with agreements and working arrangements negotiated by the Surgeon General with such public agencies and in accordance with contracts into which the Surgeon General may enter. Services furnished as benefits to such other individuals shall, as far as may be practical in each area, be of the same quality, be furnished by the same methods, and be paid for through the same arrangements, as services furnished to individuals entitled to benefits under this title."

The confusion of such compensatory provisions and the extreme probability that they will ultimately be utterly unenforceable by reason of the complicity and obvious entanglements inherent in the scheme, may readily be appreciated, and may well strike terror to the hearts of State Health Administrators who are not without some unhappy experiences in the administration of sundry other Federal-State legislative acts.

A second means test appears under the caption—"Medical Care for Needy Persons," on page 28, beginning with line 4, to wit: (8) "Provide that the State agency shall, in determining need for medical care, take into consideration (A) the requirements of individuals claiming medical care under the plan, and (B) ANY INCOME AND RESOURCES of an individual claiming medical care under the plan, which must be taken into consideration with regard to an individual claiming assistance under a State plan approved under the Social Security Act, as amended."

The following Section 133, (b) (2), also concerns itself with the financial testing of needy persons with a closing paragraph relating to a means test for the dead, to wit: "Provided, That any part of the amount recovered from the estate of a deceased recipient which is not in excess of the amount expended by the State or any political subdivision thereof for the funeral expenses of the deceased shall not be considered as a basis for reduction under clause (B) of this paragraph."

Thus it will be seen that certain means tests are found in the proposed Act, but afar from the usually acknowledged purposes of such eligibility requirements, are to be applied to the lowest stratum of society, the poor, the needy and the unemployed, while the individual, to whom a means test should in all equity and justice be applied, is utterly excluded from such an examination. Not only that, but the bill welcomes him with open arms to its health benefits, whether he be a bank president, a moving-picture magnate, or other "malefactor of great wealth." The invitation is extended in line 13, page 77, which states: "The term 'employee' also includes an officer of a corporation!"

In the light of these paradoxical provisions of the proposed Act, the prophetic words of Saint Matthew become crystal clear as recorded in the 25th chapter, 29th

verse of the Parable of the Talents, where is written—"For unto every one that hath shall be given, and he shall have abundance; but from him that hath not shall be taken away, even that which he hath."

The framers of the bill naively admit that strong possibility of its failure to accomplish the ends intended by actually writing into its content the following strikingly prophetic passages, to wit:

Section 204(f), page 47, beginning on line 10: "The methods of administration, including the methods of making payments to practitioners, shall—

(1) insure the prompt and efficient care of individuals entitled to personal health service benefits;

(2) promote personal relationships between physician and patient;

(3) provide professional and financial incentives for the professional advancement of practitioners and encourage high standards in the quality of services furnished as benefits under this title through the adequacy of payments to practitioners, assistance in their use of opportunities for postgraduate study, coordination among the services furnished by general or family practitioners, specialists and consultants, laboratory and other auxiliary services, coordination among the services furnished by practitioners, hospitals, public-health centers, education, research, and other institutions, and between preventive and curative services, and otherwise;----"

Testimony before this committee by witnesses fully informed as to the facts demonstrates beyond all doubt that the treatment of patients under governmental systems now in existence abroad, is neither prompt nor efficient. If the adjective "prompt" is used to denote swiftness and dispatch, observations of the working of the panel system in the average English "surgery" would fully bear out the designation of "prompt," all of which is not consonant with the designation of "efficient," but denotes an opposite relationship.

The promotion of "personal relationships between physician and patient," named in this section of the bill, implies the frank admission that the proposed Act will destroy those sacred obligations which now pertain to this confidential accord. The numerous detailed reports incident to administrative techniques, subject to the inquisitive scrutiny of hundreds of government employees, would alone jeopardize confidential relationships between physician and patient, to say nothing of the impossibility of preserving such a relationship in the fast-moving whirl of mass practice of medicine associated with assembly line methods of procedure.

In regard to the effect of the proposed act upon medical education, we would refer to the excellent summary submitted to this committee on April 17, 1946, by Dr. Victor Johnson, Secretary of the Council on Medical Education and Hospitals of the American Medical Association, in which he has outlined the historic development of medical education in the Nation to its present high level, solely through private initiative and the force of public opinion.

In contrast to this continuous trend toward higher standards and greater opportunities for the education of undergraduate and graduate physicians, Dr. Wilburt Davison, Dean of Duke University Medical School, reports the following observations concerning his study of medical education in Germany which has witnessed, under socialized medicine, the decline and fall of medical teaching with total destruction of the high standing once the enviable position of German medicine and formerly acknowledged throughout the world. This study was made at the behest of the U. S. Army. (Trans. of the Association of American Medical Colleges, Vol. 21, No. 3, May, 1946.) Dr. Davison reports as follows:

"The German medical schools, which were good in 1912, have not kept pace with the advances in medicine. Except for an occasional specialist who has become famous, the German graduates, even those who took postgraduate work as assistants, are not equal to the average American senior medical student. The reasons are: Lectures without adequate laboratory and clinical work; too many

students with little or no selection (of the 6,000 total university students at pre-war Munich, 4,000 were medical); inadequate facilities; and faculties which are too small, the members of which do not know modern non-German medicine, whose salaries depend upon the number of their students so that they are tempted to encourage an increased enrollment, who also examine their own students and thus may lower standards, and who have too much private practice. Furthermore, the segregation of research workers from the medical schools into Kaiser Wilhelm Institutes has reduced the productiveness of German medicine so that the medical journals for a generation have been of little scientific value. As a result, although accurate figures are not available, German physicians, in addition to being poorly trained, are too numerous. Unfortunately most of the Germans do not realize that improvement, reorganization, limitation and supervision of medical education are necessary."

Munich is a word made infamous throughout the civilized world as expressive of weakness, intrigue, and failure. It may now assume the honor of representing the German center of diploma mills to supply the "panel doctors" needed in their system of socialized medicine although they possess only the qualifications of the average fourth year American medical student!

As to the status of graduate physicians in England, the Secretary of the British Medical Association, several years after the institution of State medicine in that country, admitted that the Ministry of Health had to form classes to educate physicians through postgraduate courses because of their lack of knowledge in the care of children.\*

The Academy of Pediatrics would ask the framers of the bill what constitutes a "practitioner," as the term occurs in the pages of the proposed Act?

If the health and lives of young infants and children, who are entirely bereft of the ability to exercise judgment in the choice of a physician, will be entrusted to the tender mercies of cultists, pseudophysicians, and various ill-trained camp followers of the profession of healing, what of the evil results upon the health and lives of the young of our country?

Throughout the bill there is no definition or designation as to what constitutes a "physician" or a "practitioner," but a number of terms are used which vary in verbiage and significance.

The following variations occur:

Page 44, lines 2 and 3: "general or family practitioners."

Page 45, lines 14 and 15: "practitioner or group of practitioners."

Page 45, line 22: "the practitioners."

Page 46, line 8 et seq: States, "In establishing such standards and in designating such specialists or consultants the Surgeon General shall utilize as far as it is consistent with the purposes of this title standards and *certifications* developed by competent professional agencies and shall take into account the personnel resources and needs of regions and local areas." This phraseology evidently limits the selection of specialists and consultants to persons holding the degree of doctor of medicine as such as the only practitioners of the healing art who are subject to "certification" by duly accredited boards of examiners in the various specialties.

Page 47, line 1, occurs: "The names of medical and dental practitioners."

Page 47, lines 5 to 9: "Such lists of names shall include general or family practitioners and qualified specialists and consultants, respectively, and with respect to qualified specialists and consultants the class or classes of specialist or consultant services for which each has been qualified."

Page 48, lines 9 and 10. Herein first appears the phraseology: "general medical and family practitioners." Does this wording designate holders of the degree of doctor of medicine only, who are to receive "payments from the Account"?

\*Personal interview with the writer.

*of the population unable to pay for medical services, to the end that the standards of medical care may be maintained at a high level among such groups.'*

"The Academy of Pediatrics does not favor the use of Federal funds for those able to provide good medical care from their own resources.

"The Academy directs the attention of those considering proposed legislation to its fact-finding study of child health services now in progress which, at its conclusion, should assist in the development of sound programs at state levels based on demonstrated needs.

"Pending the completion of this study, it is recognized that urgent needs exist in some states that should be met in the immediate future. To this end the Academy recommends that additional Federal funds be made available for grants-in-aid to the states under existing Maternal and Child Health and Crippled Children's programs of Title V of the Social Security Act, as amended in 1939.

"The Academy would welcome the privilege of sending its representatives now or at any time to confer with those responsible for the preparation of legislation pertaining to child health."

Dr. Martha M. Eliot requested me as chairman of the committee on legislation, if it met with my accord, to write to Chairman Doughton of the House Ways and Means Committee asking that the limitations now existing in the Social Security Act, as amended, relating to appropriations under Title V, Parts 1, 2, and 3, be lifted to assure larger funds for the administrations of this title.

Inasmuch as the Academy asked additional funds for these purposes under the resolutions introduced by Vice-President Hill at its last meeting and adopted by the Academy, the following letter was written to Congressman Doughton and acknowledged by him upon its receipt:

May 21, 1946

Honorable Robert L. Doughton,  
Chairman,  
Ways and Means Committee,  
House of Representatives,  
Washington 25, D. C.

Dear Mr. Congressman:

It is my understanding that the Ways and Means Committee now has under consideration certain changes in the Social Security Act, including the possible removal of the present limitations on sums appropriated in connection with carrying out the purposes of Title V, Parts 1, 2, and 3, relating to maternal and child health services and crippled children.

As the representative of the American Academy of Pediatrics, a national organization of children's physicians, and the chairman of its committee on legislation, I would respectfully call to the attention of your committee the urgent recommendations of this body concerning the provision of adequate funds by the Federal Government to assist the States, "especially in rural areas and in areas suffering from economic distress," by enabling the Children's Bureau which administers Title V, Parts 1, 2, and 3, to fulfill the functions demanded of it by the provisions of the Social Security Act.

This Federal Bureau, since the creation of the Act by the Congress, has carried out its obligations relating to maternal and child health and care of crippled children through arrangements with the State agencies in an exemplary and highly satisfactory manner, being handicapped only by the limitations in the funds available for these purposes.

The Academy of Pediatrics believes that the statutory provisions of the organic Act now under your consideration would fulfill the needs, where need is

demonstrated, of mother- and children if adequate appropriations were made by the Congress to accomplish the objectives of Parts 1, 2, and 3, of Title V, without the necessity of the passage by the Congress of several legislative proposals now pending which are of questionable utility, as evidenced by the pronounced opposition developed by committee hearings.

I would submit for the consideration of your committee the following resolutions adopted by the American Academy of Pediatrics at its annual meeting in Detroit, January 15-18, 1946, to wit:

The American Academy of Pediatrics in annual session at Detroit, Michigan, January 15-18, 1946, after careful consideration of proposed legislation in Congress as it relates to child health services reaffirms its resolution as adopted at its 1939 session, namely:

"That the American Academy of Pediatrics, regarding the provisions for maternal and child welfare, favors the use of public funds to provide such services to those groups of the population unable to pay for medical services, to the end that the standards of medical care may be maintained at a high level among such groups."

The Academy of Pediatrics does not favor the use of Federal funds for those able to provide good medical care from their own resources.

The Academy directs the attention of those considering proposed legislation to its fact-finding study of child health services now in progress which, at its conclusions, should assist in the development of sound programs at State levels based on demonstrated needs.

Pending the completion of this study, it is recognized that urgent needs exist in some States that should be met in the immediate future. To this end the Academy recommends that additional Federal funds be made available for grants in-aid to the States under existing Maternal and Child Health and Crippled Children's programs of Title V of the Social Security Act, as amended in 1939.

The Academy would welcome the privilege of sending its representatives now or at any time to confer with those responsible for the preparation of legislation pertaining to child health.

Respectfully submitted,

JOSEPH S. WALL, Chairman,

Committee on Legislation

American Academy of Pediatrics.

The report of the Committee on Legislation was accepted and it was voted that a letter of thanks be sent to Dr. Joseph S. Wall for his work in appearing before the Senate Committee representing the American Academy of Pediatrics.

#### Report of the Committee on Mental Health

The Committee on Mental Health expects to complete the motion picture "Mental Growth During the First Two Years of Life" this summer.

Respectfully submitted,

BERT I. BEVERLY, Chairman

This report was accepted.

#### Report of the Committee on Latin-American Scholarships

It has long been the desire of the members of this committee to have an exchange of fellows with the Latin-American countries. The chairman, having visited the city of Mexico, realized the quality of service that was being rendered in the *Hospitale Infante* and, at the time, Dr. Gomez suggested the possibility of one or two Americans coming to Mexico. It has since been in the mind of the committee that such an arrangement might be very beneficial.



At a recent meeting of the Public Health Committee of the Kellogg Foundation, the executive staff of the Foundation expressed its willingness to finance two such scholarships, allowing for payment of transportation to and from Mexico City as well as a monthly stipend. When this offer was communicated to Dr. Gomez, he was very willing that such be the case and included in his letter a note from the official authorities of the hospital saying they were offering places to two young American physicians who might want to come to the hospital to spend eighteen months as interns. They would give room, laundry, board, and training in the medical and surgical pediatric field.

The mode of selection of the fellows has been taken under advisement by your Committee and the relationship of such service as credit by the American Board of Pediatrics' Examiners will be determined.

Respectfully submitted,

HENRY F. HELMHOLZ, Chairman

The report of the Committee on Latin-American Scholarships was accepted. It was moved, seconded, and carried that we recommend to the American Board of Pediatrics that they consider the Children's Hospital in Mexico City a good place of training for American physicians.

Dr. Clifford G. Grulee reported meeting with the Committee on Pediatric Awards at the American Pediatric Society meeting at Skytop, Pa., and discussing with them several phases of their work. This committee is quite active and will report its decisions at the meeting in Pittsburgh.

Dr. Edgar E. Martmer reported his activities as chairman of the Program Committee with respect to the program.

#### **Report of the Committee on Geographical Distribution of Pediatricians**

On account of the recent epidemics in Cleveland and vicinities, our activities in the work have been curtailed. There have been some delays in answering letters referred to me by your office.

The work on a revised map together with clearing the desk of delayed correspondence is the plan for the next few months, and I am hoping to be up to date shortly.

A questionnaire to the various pediatric hospitals and pediatric departments of these hospitals, relative to recent or prospective graduates interested in locations with Fellows of the Academy of Pediatrics who are looking for suitable assistants in their private practice, would be timely and would help the Fellows in their search for such qualified men.

Respectfully submitted,

OTTO L. GOEHLE, Chairman

The report of the Committee on Geographical Distribution of Pediatricians was accepted, but it was decided that it would not be wise at this time to send out a questionnaire.

#### **Report of the Committee of Mother's Milk Bureau**

My correspondence from members of the Committee of Mother's Milk Bureau sums up reports on the difficulties experienced in various localities in obtaining the services of mothers able and willing to furnish breast milk.

The committee members are united in the thought that there is a necessary place for breast milk in infant feeding. Furthermore, the question has arisen as to whether this Academy should not start a publicity campaign in favor of breast feeding.

The committee is asking for a place on the program of the Pittsburgh meeting for the discussion of Breast Feeding and Mother's Milk Bureaus, leaving it to your judgment as to the best place to present them.

Respectfully submitted,

JULIUS H. HESS, Chairman.

This report was accepted.

**Report of Committee on Rheumatic Fever**

Following the meeting of this committee in Detroit in January, a few members met in New York in April at the time of the Region I meeting to discuss the Statement on Rheumatic Fever which was submitted to the Executive Board and which was not unanimously approved. By recommendation of the committee members present, this statement is now under revision, and will be cleared by our Committee and the School Health Committee. This latter committee had a joint responsibility in the framing of the original statement.

Two of the members of the committee, as members of the Rheumatic Fever Advisory Committee of the Children's Bureau, met in Washington, D. C. on April 29 and 30 to review the present status of State rheumatic fever programs; to discuss methods for their evaluation; to explore needs and trends in the future expansion of these State services; and to review policies of the Children's Bureau relating to the rheumatic fever program. This conference was most provocative and from it came certain recommendations from the Advisory Committee.

It has been thought wise and timely to hold a conference for professional groups in the near future. The subject would be Rheumatic Fever and the conference would be sponsored by the Academy of Pediatrics. To it would be invited all the national groups within the Council of Rheumatic Fever and any other groups which might contribute to its success.

Respectfully submitted,

ALEXANDER T. MARTIN, Chairman

This report was accepted.

**Report of the Committee on National Defense**

I have just learned from the United States Committee for Care of European Children that additional groups of children are to arrive in this country shortly. They are to be housed in a reception center in New York City where pediatric examinations and care will be required. As you know, in the past the Committee on National Defense has undertaken the examination and routine care before placement. I understand that several hundred children are to be included in this quota, and Dr. Stimson and I will obtain the services of pediatricians for the medical care of these youngsters.

Respectfully submitted,

CARL H. SMITH, Chairman

This report was accepted.

**Report of the Committee on Postwar Courses in Pediatrics**

Total number desiring refresher courses	39
Total number desiring residencies	283
Total	<u>322</u>
Men placed in residencies	98
Men placed in refresher courses	19
Number desiring refresher courses but not heard from	13
Number desiring residencies but not heard from	111
Total	<u>124</u>
Number desiring refresher courses on active list	26
Number desiring residencies on active list	169
Total	<u>229</u>

There are approximately ten refresher courses being offered.

There is only one residency being offered this year. There are approximately 30 being offered for 1947. How many of these are already filled we do not know.

Equivalent courses are being offered at the following institutions:

Babies Hospital (Coit Memorial), Newark, N. J.

Knoxville General Hospital, Knoxville, Tenn.

Hartford Hospital, Hartford, Conn  
 Raymond Blank Memorial Hospital, Des Moines, Iowa  
 Roosevelt Hospital, New York, N Y  
 Germantown Dispensary, Germantown, Philadelphia, Pa  
 Graduate Hospital of University of Pennsylvania, Philadelphia, Pa  
 Western Pennsylvania Hospital, Pittsburgh, Pa  
 St. Luke's and Children's Medical Center, Philadelphia, Pa  
 St. Joseph Hospital (Creighton Memorial), Omaha, Neb  
 Franklin Hospital, San Francisco, Calif  
 Babies Hospital of Wilmington, Wilmington, Del  
 Mt Sinai Hospital, Chicago, Ill  
 Beth Israel Hospital, New York, N Y  
 Brooklyn Hospital, Brooklyn, N Y  
 Hermann Hospital, Houston, Texas  
 Salem Hospital, Salem, Mass  
 Presbyterian Hospital, Charlotte, N C  
 Steinberger Hospital for Women and Children, Greensboro, N C  
 Rex Hospital, Raleigh, N C  
 St. Michael's Hospital, Newark, N J  
 Rochester General Hospital, Rochester, N Y  
 Jewish Hospital, St. Louis, Mo  
 Children's Mercy Hospital, Kansas City, Mo

The postage spent by this committee since December, 1945, amounted to \$64.63. Thus is approximately 2,154 letters.

Respectfully submitted,

CLIFFORD G. GRULFE, Secretary-Treasurer

This report was accepted

#### Report of the Committee on Tumor Registry

A meeting of this committee was held April 29, 1946.

The objective of this committee is the reduction of the mortality from neoplasms during childhood.

During the war our activities were limited to the collection of data upon clinical material. Since Jan. 1, 1946, the developments have been:

A statistical study of the cases in the registry is in progress.

An exhibit of childhood neoplasms consisting of photographs and statistical charts has been prepared for the use of medical groups and nonmedical groups interested in health education.

The diagnostic service of the consulting board of pathologists is again available.

A secretary has been engaged.

The clinical, pathologic, research, and statistical facilities of the Memorial Hospital for Cancer and Allied Diseases, New York City, have been made available to us.

A grant to defray our expenses during the year 1946 has been received from the American Contract Bridge League.

The committee believes the general lack of knowledge on the part of the laity that children may suffer from cancer is a serious obstacle to the attainment of our objective.

The committee therefore recommends that the Children's Bureau of the United States Department of Labor be requested to include a paragraph on this subject in its widely distributed booklet, *Infant Care*.

Respectfully submitted,

HAROLD W. DUDGEON, Chairman

HARVEY E. MARTIN

HELBERT F. JACKSON

This report was accepted

There were no reports received from the following Committees:

Committee on Contact Infections  
 Committee on Cooperation with American Legion  
 Committee on Fetus and Newborn  
 Committee on Medical Education  
 Committee on Mental Health  
 Committee on Honorary Fellows  
 Committee on Immunization and Therapeutic  
     *Procedures for Acute Infectious Diseases*  
 Committee on Nursing Education  
 Committee on a Library and Museum of Pediatrics  
 Committee on Nutrition

The question of the International Congress was discussed extensively with Dr. Henry F. Helmholtz present. It was decided to hold a meeting of Region V immediately preceding the meeting of the International Congress. Dr. Félix Hurtado was made chairman of the program committee for this meeting.

The question of a \$10.00 assessment to help finance the International Congress of Pediatrics was to be presented to the members at the meeting of the Academy at Pittsburgh. It was approved that three members of the Academy be named by the President to act on the planning committee of the International Congress.

It was voted that the Fellowship Blanks be amended to incorporate within them the service records of men during World War II.

With respect to awards of the American Public Relations Association the secretary was empowered to present our qualifications for such awards to that body at a time when Dr. Joseph S. Wall felt that it was desirable.

MEETING ADJOURNED.

The Academy received the following questionnaire from the office of Senator Murray, Chairman of the United States Senate Committee on Education and Labor, seeking an answer to the question, "What are our objections in the nation's health?" The same question had been sent out to other leading professional agencies throughout the country.

March, 1946

*Questions on*

*Health Goals for America's Future*

I. Over the next 5 years, what should be our goals on the nation's health? What should our aims be with respect to increasing the average expectation of life?

What should our aims be in reducing—

- a. the infant mortality rate?
- b. the maternal mortality rate?
- c. the death rate at various ages?

What should our aims be in preventing or controlling—

- a. heart disease?
- b. cerebral paralysis?
- c. cancer?
- d. tuberculosis?
- e. diabetes?
- f. pneumonia?
- g. poliomyelitis?
- h. rheumatism and arthritis?
- i. rheumatic fever?
- j. venereal disease?
- k. malaria?
- l. dental defects?

- m. defects of vision?
- n. defects of hearing?
- o. mental ill-health?

II. Over the next 5 years, what should be our goals on health personnel, facilities, and education?

What should our aims be with respect to the number and distribution of qualified—

- a. doctors?
- b. dentists?
- c. nurses?

What should our aims be with respect to the number and distribution of adequate—

- a. hospitals and hospital beds?
- b. health clinics and health centers?
- c. sanitation facilities?

What should our aims be with respect to—

- a. medical research?
- b. professional medical education?
- c. health education for the public?

At the meeting of the Executive Board of the Academy in New York at the time of the meeting of Region III, the following reply was formulated, approved, and sent to Senator Murray.

#### QUESTIONS AND ANSWERS ON HEALTH GOALS FOR AMERICA'S FUTURE

The American Academy of Pediatrics is the national society of physicians especially trained in the care of infants and children. It is the outgrowth of the American Child Health Association and has for its purposes the promotion of the health of children and support of various medical activities in the field of pediatrics.

This group wishes to present the following reply to the questionnaire presented to it by Senator Murray in his letter of March 18, 1946.

#### *I. Over the Next 5 Years, What Should Be Our Goals on the Nation's Health?*

##### PRELIMINARY STATEMENT

Health goals for children cannot be separated from such public health and welfare measures as:

- A. Adequate housing
- B. Proper clothing
- C. Sufficient, proper food
- D. Sanitary living conditions including:
  - (1) Safe water supplies
  - (2) Proper sewage
  - (3) Pasteurization of milk
  - (4) Proper food inspection including:
    - (a) Inspection at source
    - (b) Inspection during processing
    - (c) Proper sanitary preparation for consumption.

Progress in the field of child health is directly proportional to the degree that society both individually and collectively recognizes the importance of the above-mentioned measures and takes the necessary steps to improve them.

#### *What Should Be Our Aims With Respect to Increasing the Average Expectation of Life?*

The American Academy of Pediatrics has defined pediatrics as covering the age period from birth well into adolescence usually between sixteen and eighteen years. With a reduction

in infant mortality some individuals who would heretofore have died during the first year of life can be expected to die during childhood and adolescence but the great increase in the average expectancy lies in the treatment of the degenerative diseases and the hazards of increasing age which do not fall in the field of pediatrics.

### *What Should Our Aims Be in Reducing:*

#### *a. the infant mortality rate?*

Over the next five years our goal should be to reduce infant mortality in all states to the same degree as in the States of Connecticut (29.5), Oregon (30.0), Minnesota (30.9), Utah (31.4), Idaho (32.0), New York (32.7), Illinois (33.3), Kansas (33.6), New Jersey (33.7), and Iowa (34.0). A definite and considerable reduction can be immediately brought about by the application of known facts, concerning prenatal and infant care in areas where high infant mortality rates exist.

A further reduction in infant mortality, especially during the first month of life, may be possible through scientific discoveries and medical progress and the universal application of such knowledge.

#### *b. the maternal mortality rate?*

Since pediatrics is concerned with the infant, child, and adolescent, the American Academy of Pediatrics suggests that other groups are qualified to answer this question. Reduction of neonatal deaths and reduction of maternal deaths are inextricably associated with good obstetrics.

#### *c. the death rate at various ages?*

The chief causes of death in the age group in which we are particularly interested, that is, from birth to eighteen years,\* are:

Under One Year		Age One	
<i>Causes</i>	<i>Deaths</i>	<i>Causes</i>	<i>Deaths</i>
All Causes of Death	345,925	All Causes of Death	32,760
Congenital malformations and diseases of early infancy	204,237	Influenza and pneumonia	8,494
Influenza and pneumonia	51,080	Accidents	4,641
Diarrhea and enteritis	25,800	Diarrhea and enteritis	3,837
Accidents	8,584	Whooping cough	1,707
Whooping cough	6,789	Congenital malformations	1,645
Diseases of thymus gland	3,213	Tuberculosis, all forms	1,531
Dysentery	2,976	Measles	952
Syphilis, all forms	2,626	Dysentery	676
Hernia and intestinal obstruction	1,966	Meningitis (not due to meningococcus)	548
Meningitis (not due to meningococcus)	1,939	Diphtheria	532
Age Two		Age Three	
<i>Causes</i>	<i>Deaths</i>	<i>Causes</i>	<i>Deaths</i>
All Causes of Death	16,488	All Causes of Death	11,718
Accidents	3,502	Accidents	3,054
Influenza and pneumonia	3,093	Influenza and pneumonia	1,641
Diarrhea and enteritis	1,000	Diphtheria	527
Tuberculosis, all forms	790	Tuberculosis, all forms	510
Congenital malformation-	629	Appendicitis	430
Diphtheria	601	Diarrhea and enteritis	402
Whooping cough	519	Congenital malformations	387
Measles	456	Cancer, all forms	379
Appendicitis	401	Leukemias and aleukemias	333
Leukemias and aleukemias	378	Diseases of buccal cavity and adnexa	290

\*Source: U. S. Bureau of the Census, Vital Statistics of the United States.

\*Compiled by Statistical Bureau, Metropolitan Life Insurance Company, April 11, 1946.

<i>Age Four</i>		<i>Ages Five to Nine</i>	
<i>Causes</i>	<i>Deaths</i>	<i>Causes</i>	<i>Deaths</i>
All Causes of Death	9,093	All Causes of Death	31,698
Accidents	2,530	Accidents	9,887
Influenza and pneumonia	1,112	Influenza and pneumonia	2,736
Diphtheria	428	Diseases of the heart	1,589
Appendicitis	390	Appendicitis	1,570
Tuberculosis, all forms	327	Tuberculosis, all forms	1,252
Cancer, all forms	277	Cancer, all forms	940
Leukemias and aleukemias	274	Diseases of buccal cavity and adnexa	866
Congenital malformations	270	Congenital malformations	826
Diseases of buccal cavity and adnexa	247	Diphtheria	800
Diseases of the heart	227	Leukemias and aleukemias	742
<i>Ages Ten to Fourteen</i>		<i>Ages Fifteen to Nineteen</i>	
<i>Causes</i>	<i>Deaths</i>	<i>Causes</i>	<i>Deaths</i>
All Causes of Death	30,944	All Causes of Death	58,492
Accidents	9,791	Accidents	18,445
Diseases of the heart	2,687	Tuberculosis, all forms	9,118
Influenza and pneumonia	2,217	Diseases of the heart	4,314
Tuberculosis, all forms	2,072	Influenza and pneumonia	3,074
Appendicitis	1,908	Puerperal causes	2,403
Cancer, all forms	904	Appendicitis	2,086
Nephritis, all forms	865	Cancer, all forms	1,574
Acute rheumatic fever	729	Nephritis, all forms	1,540
Leukemias and aleukemias	600	Homicide	1,525
Congenital malformations	537	Suicide	1,148

May we call to your attention the prominent position which accidents have in this tabulation.

*Infectious Diseases* (Diarrhea and enteritis, influenza and pneumonia, meningitis, diphtheria and others).—The universal application of known and proven preventive measures would materially reduce the deaths from infectious diseases. In the period from 1910 to the present, reductions in deaths from these diseases have occurred and it is reasonable to suppose that further reductions will continue.

#### *What Should Our Aims Be in Preventing or Controlling:*

##### *a. heart disease?*

Heart disease in children can be divided into two classes, congenital and acquired.

(1) Congenital heart disease. There are no known methods of preventing congenital heart disease. In controlling this type of heart affliction certain selected cases constituting a small proportion are amenable to surgical treatment.

(2) Acquired heart disease. The chief cause of acquired heart disease in children is rheumatic fever and further discussion will be found under that heading.

##### *b. cerebral paralysis?*

Cerebral paralysis in children is primarily due to cerebral maldevelopment prior to birth or to adverse conditions at the time of birth. Maldevelopment of the brain before birth cannot be prevented in the light of our present knowledge and there is little likelihood of means of prevention being discovered or applied in the immediate future. Cerebral paralysis developing at birth is in the field of obstetrics rather than pediatrics. Perhaps some results might be obtained by further education along eugenic lines and the recognition of the importance of the Rh factor in certain cases of mental defect.

##### *c. cancer?*

Cancer in infancy and childhood is not a serious problem. Other groups primarily interested in the adult are better qualified to suggest aims in the prevention and control of this important health problem.

*d. tuberculosis?*

The prevention of tuberculosis and the control of its spread is dependent upon the utilization of available medical knowledge concerning this disease. Few children need have tuberculosis if there is a universal recognition and acceptance of the importance of the prevention of contacts of the child with tuberculous individuals in the home, school, and community. An equally important measure for the prevention of tuberculosis is the adequate pasteurization and proper sanitary control of all milk used for human consumption both in a fluid state and in the various milk products. This might be helped by certification of herds of cattle.

The control of tuberculosis in children should include universal case finding facilities. The isolation of open cases of tuberculosis and the adoption of periodic health examinations for all children. Adequate means of handling tuberculous cases in sanatoria should be provided.

*e. diabetes?*

Diabetes in children does not constitute a serious problem numerically.

*f. pneumonia?*

Pneumonia in childhood becomes a problem in direct proportion to the health of the child prior to the onset of the infection. The well-nourished, well-developed individual who becomes ill with the disease responds quickly and favorably to present-day methods of treatment.

*g. poliomyelitis?*

The National Foundation for Infantile Paralysis is in the best position to speak on this subject. Continued research would appear to be the logical aim so as to develop methods of preventing this disease and controlling its spread.

*h. rheumatism and arthritis?*

Rheumatism and arthritis are diseases of adult life and are rarely found amongst children.

*i. rheumatic fever?*

As far as is now known, the prevention of rheumatic fever is chiefly dependent upon the general principles enumerated in the preliminary statement; especially, adequate housing and proper food. The disease is rarely found amongst children who are well fed and properly housed. Continued research in an effort to find the cause of this disease and methods for its control should be carried out.

The control of rheumatic fever is dependent upon its early recognition, and appreciation of the potential danger and long time supervision.

*j. venereal disease?*

The prevention and control of venereal disease is primarily a problem of early adult life. Adequate knowledge, properly given to adolescents by competent educators should be a part of the health education of all adolescents.

*k. malaria?*

The prevention and control of malaria is primarily a question of sanitation. The eradication of the *Anopheles* mosquito will prevent the spread of this disease.

*l. dental defects?*

The dental profession is best qualified to discuss this subject.

*m. defects of vision?*

The vast majority of visual defects seen in childhood are of congenital origin. Continued research should be encouraged in an effort to obtain more knowledge concerning the cause of such defects and possible means of prevention.

The control of defects of vision should include parental education concerning the importance of early recognition and the adequate care and treatment of this condition.

Facilities should be available in all schools for at least gross visual tests.



*n defects of hearing?*

The same statements made under (m) defects of vision, apply concerning hearing. Education programs for the hard of hearing should be extended.

*o mental ill health?*

(1) Mental defects for which we have no method of prevention or control. The provision for adequate custodial facilities for all such individuals should be encouraged and accelerated. Education and rehabilitation of those not idiots or imbeciles may make them useful members of society.

(2) Psychotic disturbances. Because so little is known concerning psychotic disturbance research in this field should be encouraged and expanded.

(3) Emotional maladjustments. The prevention of emotional maladjustments is dependent upon a better understanding of the importance to the child of a normal family, school and community life. Our aims should be to bring about a wider recognition of the influence of the home, school and community on the child. All schools should have access to psychological and psychiatric consultation. Mental hygiene programs, taking into account the prenatal and neonatal periods are most important preventive measures.

*II Over the Next 5 Years, What Should Be Our Goals on Health Personnel, Facilities, and Education?*

*What Should Our Aims Be With Respect to the Number and Distribution of Qualified a doctors?*

At the present time, the American Academy of Pediatrics is conducting a national survey covering every county throughout the nation to ascertain all the facilities available for the medical care of children. This is the first attempt to survey such facilities that has been made. All previous surveys have been based upon samples and the American Academy of Pediatrics does not consider that a survey conducted by the sampling method can furnish the information that its present undertaking will reveal. Too frequently such samples fail to present conditions as they exist. It was not possible to carry on this survey while the war was in progress and a survey made at that time would not have revealed conditions during normal times. With the termination of hostilities, however, preparations were immediately begun and the survey in one state (North Carolina) has already been completed and the data is now being compiled. In the other states preparations are going ahead rapidly and it is expected that these data will become available within a matter of months. With the completion of this survey, it will be possible to make more concrete recommendations in answer to the first and second sections of Part II of this questionnaire.

The present Academy survey will have some very definite information regarding the distribution of adequate medical care for children in the states.

*b dentists?*

To be answered by the American Dental Association.

*c nurses?*

To be answered by the National Nursing Societies.

*What Should Our Aims Be With Respect To*

*a medical research?*

Research investigators are born and no amount of money can provide the inherent qualities necessary in such an individual. However, such individuals should be provided with adequate facilities and funds to carry on their work. Because of the reduction from private sources of such funds, government should promote medical research by all possible means. In this connection, it is extremely important that the control and policies rest with competent persons or groups with as little governmental control as possible.

*b. professional medical education?*

The Academy survey will bring out the needs of medical education for the care of children in this country. Perhaps we may find that there are needed more or better coordinating courses in the medical schools and that postgraduate education for pediatricians and general practitioners with respect to the care and treatment of children should be promoted. It is certain that we cannot have better medical care for children until we have more physicians well trained in pediatrics.

*c. health education for the public?*

Pediatricians do a much better job by individual instruction to the mother than can be done when instructing a large group of individuals because these problems are individual problems. As the number of pediatricians increases this health education to the public will increase. In those centers in which pediatric care for children has been stressed over a longer period, the results have been in the main the best. The education of the public comes only after years of effort.

# The Academy Study of Child Health Services

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It has been clearly demonstrated from the experience to date that a group of physicians, practitioners in a field of medicine, can carry on a so called study or an investigation of their own activities with the object of putting their house in order. It has furthermore been shown that a group of clinicians can work effectively and harmoniously with Federal agencies which, by virtue of their established organization, are experts in techniques and have the advantages of experience in the field of analysis and the accumulation of data. Both the Federal agencies, the Children's Bureau and the U. S. Public Health Service, and the American Academy of Pediatrics realize that "isolationism" in the future progress of medical care cannot exist. The evidence of the awareness of this united front is one of the most encouraging and important observations of the Study to date and cannot be overemphasized.

With these facts in mind and the organization fully developed and launched on a national scale, the time has come when we who are actually making the investigation must ask ourselves, "What are we going to get out of this? What do we want to show from this elaborate undertaking?" We must continually have our eye on the beam and our sights lifted upon our target. It is only too easy and all too common for a research worker to be confused by his technique and diversified data and never arrive at the goal and objective of his study. This danger is one of which we must be continually aware. With the tremendous expenditure of funds, the multitudinous and somewhat involved schedules, it would be very easy to lose sight of our objective and not see the forest for the trees. Before giving consideration to the anticipated conclusions of our Study, the membership of the Academy should bear in mind that there will inevitably be many disappointments as the investigation reaches completion. We undertook this Study with little idea of what it entailed. No one connected with the original committee who presented the program to the Academy had ever had any firsthand experience in a statistical study of this kind and magnitude. Certainly we had no realization of its cost. We were unable to find a person who had had experience in directing such an effort and were obliged to develop one, and in this, I should add, we have been successful. The Study was put in our laps—it had to be done. No one can ever question the vision of the Academy in accepting the responsibility and opportunity in the interests of medical care for children. In spite of our many handicaps and especially our lack of experience, we predict that the disappointments and unanswered questions will be outweighed by positive findings which will direct the future development of medical practice in the care of children.

Many of the results of the Study are already known. Some are impressions, and impressionistic knowledge is dangerous. Perhaps one of the most urgent needs and most anticipated information concerns degree and distribution of medical care for children. If our thesis is correct that medical care for children increases their potential development, it follows that this should have wide distribution and be made available to all. It is very easy and impressive to make maps showing that pediatricians are located in urban communities, but this by no means answers the question whether the children of our cities are having medical attention commensurate with our standards of pediatric care of today. It seems highly probable that in our own backyard we will find flagrant instances where hospitals are overcrowded, where premature infants, for instance, are receiving inadequate care, where facilities and trained personnel are not available. The members of the Academy expect to receive factual data concerning these matters and anticipate recommendations for their improvement.

One of the most urgent and pressing results of the Study concerns the distribution of medical care on a national geographical scale. Many of us have little or no idea at present concerning the care of children in states outside our limited horizon. We are certain that the mortality of infants and children in states with a high percentage of Negro population in the South is greater than in states of higher income groups, but we have never taken adequate

measures to rectify this condition. We are justified in expecting that our Study will reiterate and conclusively show the level of medical care in these states and, because these data were collected by practicing physicians, an added impetus for improving medical care and facilities is predicted.

One of the questions we must answer from our investigation is closely related to distribution of medical care and concerns the technique of practice. Is the average pediatrician of today working effectively in the light of the needs for medical care, both in his community and the states at large? Is he making too many and unnecessary visitations or is he making too few? Certainly many trained pediatricians are running in circles and are groping for a technique of practice that will give them financial security and a feeling of a medical *fait accompli*. Certainly if our Study shows the spotty distribution of medical care which we anticipate, then some new and better technique retaining the principle of free enterprise must be formulated. One has a right to ask if the trained pediatrician, in the light of the present needs, is justified in carrying on the solo type of practice that is so common in many communities. A good business-man with an article to sell studies areas where his product is needed. If it is a razor, he teaches the unshaven to shave and works out a technique for the wider distribution of his razor. Our Study should awaken such objectives in us who have had certain medical training for the care of children. Furthermore, the realization of these objectives should not be the sole responsibility of Federal agencies but a cooperative effort of pediatricians and agencies.

We have, therefore, now arrived at a most critical period of our investigation which should contribute to the better care of children on both a national and state level. It is a period when we must critically analyze these data which we have collected through our personal efforts. We must formulate again the questions which we consider should be answered. The data will be handled by expert statisticians, but they must know what we expect to learn from the collection of the material. Some of our results may not lend themselves to analytical methods but will be reported descriptively. These are problems to which your Executive Staff of the Study are now giving their attention. Soon many of the findings of the North Carolina Pilot Study will be presented to the Academy and it is hoped that through discussion and suggestions of our members we will be able to formulate a final report which will adequately utilize these data and permit us to inaugurate intelligently a constructive program for the better care of children.

WARREN R. SISSON.

# The Social Aspects of Medicine

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Dear Dr. Park:

The enclosed report on Russian Public Health and Soviet Medicine by Dr. Smorodintzev to Mrs. Berezowsky while he was at the Rockefeller Institute on a recent visit to this country seems to me interesting enough to deserve publication. Mrs. Berezowsky tells me that she has no objection to its being edited in order to make it appropriate for some particular journal. It occurred to me that with editing you might be able to use it in your column.

Sincerely,

ALLAN M. BUTLER, M.D.

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## RUSSIAN PUBLIC HEALTH AND SOVIET MEDICINE

DR. ANATOL SMORODINTZEV\*

AS TOLD TO ALICE BEREZOWSKY

Until 1919, Russia was, from the medical point of view, a potential danger of the first magnitude to Europe. Russia was the stopping off place for the epidemic diseases which moved West from the Far East, China, and India. Cholera, typhus, and smallpox, as well as other epidemic diseases, ravaged the Russian population and only the strictest border control stemmed their advance upon Europe. Even the dread plague, which comes especially from India and China, existed in our country. As far west as St. Petersburg, there were epidemics of cholera. There was no obligatory vaccination for smallpox. Regularly each year there was an average of 200,000 cases, with 40,000 mortalities. The general mortality rate in Russia was 29 per 1,000. The average life span was only 40 years. One-half of Russia's children contracted infectious diseases before the age of one year. Only one-third of the children born survived. The only favorable factor was the very high birth rate; mothers having from six to ten children. But motherhood was a frustrating process for the women of Russia and they were weakened by it.

The sanitary conditions in Russia were appalling. Good water supply was practically unknown. Even in Moscow and St. Petersburg, a great many people drank water directly from the Neva and Moscow rivers. Typhoid and dysentery were everywhere. The incidence of syphilis was high. In contrast to the United States much of it of a nonsexual origin, owing to the extremely primitive mode of life and low state of sanitary culture in the rural districts where a man who contracted syphilis infected his entire family with the disease. In primitive regions such as those where the Bashkirians and Tartars live, a high percentage of the population was infected.

In Czarist times, the cause of Russia's frightful health conditions did not lie with the medical and scientific men themselves. The fault was that a corrupt and inefficient bureaucracy gave our medical and scientific men almost no support. State medicine, although it existed, was never given sufficient funds to accomplish even a fraction of the necessary work. Only private charitable contributions made possible the greater part of whatever constructive and beneficial work was done in clinical and preventive medicine and scientific research. Starved for funds, the Department of Public Health did little for the prevention of infectious diseases; all matters of public hygiene were, for the most part, neglected.

Before the revolution, there were only twelve medical schools in all Russia. For a population of upwards of 170,000,000, there were less than 25,000 doctors, that is, about

\*Winner, 1941, of the first Stalin Prize for distinguished service to the Soviet Union, and now Chief of Department of Bacteriology Parker Institute of Leningrad and an Executive Director of Institute of Experimental Medicine.

one for every 8,000 people. But of these 25,000 doctors, 50 per cent lived in the big cities and were in private practice. Therefore, in many regions, especially the northern and eastern districts, there was sometimes only one doctor for every 20,000 of the population.

After the revolution, the whole medical picture was changed by the issuance of a government statement: *"Medical Affairs Are the Responsibility Not Only of the Medical and Scientific Branches But of All Branches of the State: Economic, Cultural and Industrial."* Thus it was clearly established that it was the duty of the economists to provide funds for necessary work; of the cultural branch to foster the education of medical and scientific personnel and the enlightenment of the people in all matters concerning public health; and of the industrial branch to concern itself with both clinical and preventive health protection of the workers. We medical and scientific men were given great responsibility, but we were not given more than our share . . . all the responsibility.

Almost as soon as it was established, the Soviet Government resolved to subsidize all education. Anyone who wanted to study medicine or science could do so without expense. Now, in Soviet Russia, a student receives not only his education free of charge, but he is also paid a salary sufficient to cover all the necessities of his life while learning—food, rent, books, and clothing.

Those students who are interested in gaining a higher education (and the possibility is open to all) decide what future field they want to enter during the last two years of their attendance at middle school, the equivalent of American high school. As soon as a student in middle school shows an aptitude or inclination toward a certain branch of learning, he is encouraged by the State to pursue it, to go on and acquire a higher education, and then to engage in postgraduate work. The standards for the selection of students for superior education are high. They must do excellent work, not only in the subjects in which they are especially interested but in all their academic studies. If they are graded "excellent," and about 5 per cent are, they can enter the higher institutions of learning without examination. Those students who do poor academic work are channeled off into occupational and industrial schools. Those who do fair or average work are given three to four years additional study in order that they may become what we call "middle personnel," that is, assistants to the top men in every field. The more a student excels, the more money the government spends on him, paying him a higher salary and enabling him to become a specialist. For a specially gifted student, increased stipendiums are given which equal the salary of a young medical doctor, a graduate. There are thousands of such students in Russia, in all branches of learning.

Our medical students receive their M.D. degrees at the age of 23 to 25 years. Then, in return for what the State has done for them, they are required to work for the State for three years, but they receive a full salary. This is an obligation they are happy to fulfill. The only duty of the newly graduated doctor is to go where he is needed most, which is usually somewhere near his university. After his State service is done, he can choose where and what he would like to do. Unless he wishes to undertake special work where the opportunity for study and practice is in only one place, the young doctor or scientist usually elects to go back to the community he came from, where his home, family, and friends are. Then he sets about earning his living, generally in State service.

Prior to the war, the average doctor was paid by the State 650 rubles monthly. As he progresses, a doctor's salary is raised about 50 per cent. Doctors of Science (Ph.D.) receive treble the minimum salary, about 1,200 to 1,800 rubles a month. A professional person can also increase his earning by doing extra work. He can attach himself as consultant to an organization other than that with which he is officially connected and receive a consultant's fee. He can also engage in writing and lecturing and such activities. All extra work entitles a doctor to extra compensation from those interested in obtaining his services, institutions, publishers, and such. Every six months to a year, a doctor is encouraged to visit one of the big district Institutes for Post-Graduate Medical Study developments. At the age of 55, he is entitled to retire on government pension. If he

wishes, a doctor can enter private practice without forfeiting his pension. His earnings as a private practitioner are subject to progressive taxation very much like American taxation on earned income. There is, however, no compulsory age of retirement.

There is a widespread belief outside Russia that there is no private practice of medicine in our country. This is not true. Every doctor can, if he so desires, enter private practice immediately on completion of his three years' practical service to the State. A small percentage do so. However, since exactly the same medical service is open to all citizens of Russia at no cost, very few patients choose to go to a private physician and pay for medical care. Those who do are most likely to choose not a young doctor but an experienced practitioner who has retired from State service.

There is also widespread belief that in a system of socialized medicine such as we have in the U.S.S.R., a patient cannot choose his or her physician. The contrary is true. Once a patient is registered at a polyclinic or medical institution, he is encouraged to choose the doctor in whom he has the most confidence. Doctors are taught to give individual consideration to their patients, to encourage mutual understanding and familiarize themselves with their patients' backgrounds and personal situations.

Concerning Soviet medicine, the most incorrect assumption of all is that Russia's prerevolutionary men of science and medicine were discarded or liquidated by the Soviet Government. All Soviet medicine was built on the nucleus that existed in Czarist times. Immediately upon the revolution, Lenin issued an appeal to all men of science to cooperate with the government. He told them that their possibilities for doing constructive work would be better than ever before and he promised them they would be free from all private worries in money matters. The great majority of professional men accepted. Those who rejected his invitation were, for the most part, very old and very conservative.

Take the case of our famous physiologist, Pavlov. For the first ten years of the Soviet regime he did not accept socialism. But he continued his work undisturbed. It was during the years 1925 to 1930 that he began to change his opinion. During the last years of his life, he became very enthusiastic about socialized medicine. At the International Physiological Congress held in Moscow in 1935, he made a speech to the assembled scientists, and said: "The only thing I fear is that I will not live long enough to repay in some measure the Soviet Government for the great attention they have paid to Science."

Today, in the U.S.S.R., more than 50 per cent of the members of our Academy of Science (the most distinguished body of its kind in Russia) were professional persons in the Czarist regime. This is true of its president, Vladimir Komaroff. The Chief Surgeon of the Red Army, Burdenko, was an important man in Czarist army medicine. In fact, it was around a nucleus of the members of the Medical Military Academy (founded by Peter the Great) that we assembled our entire military medical service.

The results of the Soviet Government's organization of science and medicine and of its fight against epidemic diseases were in evidence from 1926 on. By 1933 and 1934, we had almost eradicated smallpox by establishing compulsory vaccination. Each year we give more than 10,000,000 immunizations. Today, if I wanted to show a medical student a case of smallpox, I would have trouble finding one in all Russia. We have almost eradicated plague and cholera, despite the fact that the prevalence of these diseases among the masses in China and India is a constant danger to us. Typhus, the fatal enemy of our people during and after World War I, no longer exists as a problem. From the medical point of view, the U.S.S.R. has, since 1919, performed a service for the Western world similar to that which Russia rendered in the time of Genghis Khan. She has completely repelled the Asiatic invaders, in this case, not men but diseases.

As I said before, in 1919, we had twelve medical schools in all Russia. Now we have sixty. Leningrad and Moscow each have four medical schools, each of them independent of the other. Every year each graduates from 500 to 600 students. In the last years before World War II, we graduated 25,000 young doctors annually. In 1941, an extremely difficult year owing to the invasion of our country by the Germans, we nevertheless graduated 18,000 doctors. In 1942, there were 24,000. In 1943, there were about 30,000, which was more than ever before.

In Czarist Russia there was only one school where women were permitted to study medicine. That school was very expensive and only the minority of women interested in science and medicine could attend. After the revolution, every medical school in Russia was opened to women students. Before World War II, 60 per cent of our medical students were women. During it, for obvious reasons, 90 per cent were women. We have found that women make just as fine doctors as men. Practically the entire field of pediatrics, for example, has been taken over by women. The only branch of medicine which is less popular among women is major surgery—that is for physical reasons, not mental.

When Hitler came into power, we Russians were sure that war would come. We knew that in modern war it is not possible to have military success without good epidemic control in the rear. We realized that in order to have wartime medicine there must first be peacetime medicine. We were also fully persuaded that a healthy army can be produced only by a healthy people.

One of our greatest contributions to wartime medicine was a peacetime medical development, the blood bank. As soon as it was scientifically established in the early nineteen-thirties that blood transfusions were beneficial to traumatic surgical cases, we conceived the idea of the blood bank. Owing to cooperation between the cultural and scientific branches of the government, we had no difficulty in establishing the bank and convincing people of their moral obligation to donate blood. From then on, we have always had more donors than we could accept.

It is entirely owing to the tremendous strides we made in peacetime medicine that we were able, in a very short time, to organize an efficiently functioning wartime medicine. One of the most important factors in its success was the great amount of "middle personnel" we trained in peacetime. Today, there are available three assistants for each doctor. Our successes against Germany are attributable not only to the Red Army, but also to the high state of development of medical science both in the army itself and in the rear.

Today, despite all we have been through, the incidence of epidemic disease in Russia is not a single per cent higher than it was before the war! We accomplished this while we were fighting against almost the full might of Hitler's divisions, the slave labor of most of Europe, and in the face of the difficulties attendant on the transfer of great numbers of our population, when millions of people were on the move. In the West, after war came, we had to evacuate entire regions of all possible medical equipment and personnel in the same manner we transported our industry away from the invaded areas to the Urals, Siberia, and the Far East.

The record of our care of war casualties shows that of every 100 wounded men and women, 78 per cent were able to fight again. Only 22 per cent were lost to the Armed Forces.

For scientists and medical men there is very little difference between war and peace from the professional point of view. We always conceive our medical duty as being the same as in battle; we are obligated to give all necessary help to our people. The chief purpose of medicine is to make people physically perfect. The aim of our Russian men of science is to make both ourselves and the quality of our work better and better. We have already accomplished much, but there is as much again and more still to be done. We have conquered typhus, but we have not conquered influenza. We have wiped out smallpox, but we know very little about measles and scarlet fever, very serious diseases for children.

When transportation is easier, we Russian scientists and medical men look forward to the closest possible cooperation with our American colleagues. In America you had a perfectly organized wartime medicine. You had the best equipment and the best doctors.

Everywhere, men and women of science are agreed that the chief purpose of medicine is to make all human beings as physical perfect as possible. And after all, a sick person is a sick person, rich or poor, in war and peace.



## Academy News and Notes

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The Nominating Committee of the Academy of Pediatrics which was recently appointed by the President, feels a very serious obligation in the selection of candidates for the various offices of the Academy to be presented to the membership at the next annual meeting. Never was there a time in which the necessity for outstanding leadership was so pressing. Office in the Academy should not be a decoration for past performance but should be a pledge for future endeavor and for vigorous leadership.

Your committee hopes to have the advice of the entire membership in the selection of these candidates and requests that members write their suggestions regarding the candidates to any member of the committee: Wyman C. C. Cole, Preston A. McLendon, Howard J. Morrison, or Edward B. Shaw (Chairman).

The following members of the Academy have been released from service:

### *Army*

Horst A. Agerty, Wynnewood, Pa.  
Fred H. Allen, Jr., Holyoke, Mass.  
Warren F. Belknap, Detroit, Mich.  
Sidney S. Chipman, Norwalk, Conn.  
Vincent Del Duca, Camden, N. J.  
A. S. Finkelstein, Newark, N. J.  
Sidney Gelman, Paterson, N. J.  
Arthur Heyman, Newark, N. J.  
Clinton Hollister, Santa Barbara, Calif.  
Albert M. Jones, Memphis, Tenn.  
Morris Y. Kiosnick, New Haven, Conn.  
Aims C. McGuinness, Philadelphia, Pa.  
William G. Motel, Chicago, Ill.  
Charles E. Muhleman, La Porte, Ind.  
Norman K. Nixon, Beverly Hills, Calif.  
Victor Rudomanski, Kearny, N. J.  
Samuel Schwartz, Washington, D. C.  
Joseph F. Siegel, Washington, Pa.  
Hugh Wellmeier, Piqua, Ohio

### *Navy*

Harry H. Horwitz, Oakland, Calif.  
A. S. Hurt, Jr., Richmond, Va.  
Abiam Kanof, Brooklyn, N. Y.  
John A. Lichty, Jr., Rochester, N. Y.  
William T. Maxson, Lexington, Ky.  
A. Lane Mitchell, Houston, Texas  
Leonard B. Outlar, Wharton, Texas  
Jack E. Strange, New Orleans, La.  
Wallace B. Taggart, Dayton, Ohio  
Alvin B. Williams, San Jose, Calif.

The following members have been released from the United States Public Health Service:

Katharine G. Dodge, New York, N. Y., and  
Samuel Hurwitz, San Francisco, Calif.

Lieutenant Commander Milton Kunzrok has been promoted to Commander in the United States Navy.

## News and Notes

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Grants of over \$486,000 for the study of tropical diseases, virus diseases, biochemistry, nutrition, physiology, and other subjects in the field of medical and physical sciences, made by the John and Mary R. Markle Foundation during 1945, are announced in the final report of John A. Ferrell, medical director of the Foundation, who retired on July 1. The grants include appropriations to sixty two universities, medical schools, research institutes, schools of public health, and other research agencies.

Effective July 1, John M. Russell, former assistant to President James B. Conant of Harvard University, will become executive director of the John and Mary R. Markle Foundation. His appointment follows election to a vice-presidency of the Foundation in April of this year.

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Dr. Hart E. Van Riper, of Scarsdale, N. Y., has been appointed medical director of the National Foundation for Infantile Paralysis, Inc., it was announced by Basil O'Connor, the organization's president. Dr. Van Riper has served as acting medical director since January. The appointment was made to fill the vacancy created by the death of Dr. Don W. Gudakunst earlier this year.

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The increased funds made available to the Children's Bureau during the closing days of this congressional session will make it possible for some expansion in staff to take place. Positions are open in the division which administers grants-in-aid to States for maternal and child health and crippled children, and in the division concerned with research in the health field.

In the administrative program there are 4 or 5 openings for pediatricians with special training in various phases of clinical pediatrics such as care of the premature infant, rheumatic fever, and school health to act as consultants on the staff of the Children's Bureau. There are also several openings for pediatricians with public health training, or experience, or both, in regional offices of the Children's Bureau.

In the research field there are openings for a pediatrician with experience and special interest in the treatment of cerebral palsy, and one with an interest in special testing procedures for examination of school-age children.

All positions require basic training and experience equivalent to that required for certification by the American Board of Pediatrics. Interested persons may write directly to the U. S. Children's Bureau, Federal Security Agency, Washington 25, D. C.

## Book Reviews

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**Mitchell-Nelson Textbook of Pediatrics.** Waldo E. Nelson, M.D., Philadelphia, 1945, W. B. Saunders Company, 1,350 pages. Price \$10.00.

This fourth revised edition has been completely rewritten. There are forty-nine collaborators, each wisely chosen for his special subject, to whom the book owes most of its value. In addition to the general excellence of treatment of subject matter, the physical make-up of the single volume is particularly good. The type is easily legible in double columns on pages 10 by 7 inches, which lie flat without assistance of the reader. There are 519 illustrations of 383 figures, 26 in color, which are, for the most part, unusually good. The book will be specially useful to the undergraduate student for reading supplementary to lectures and to the post-graduate student taking "refresher" courses who has lost contact with recent pediatric literature.

A. F. H.

**The 1945 Year Book of Pediatrics.** Edited by Isaac A. Abt, D.Sc., M.D. Professor of Pediatrics, Northwestern University Medical School, Chicago. With the Collaboration of Arthur F. Abt, B.S., M.D., Associate Professor of Pediatrics, Northwestern University Medical School, Chicago. Fabrikoid. Price, \$3.00. Pp. 448, with 113 illustrations. Chicago, 1946, The Year Book Publishers, Inc.

The annual appearance of this digest of the more important original articles in medical journals makes an excellent review of current pediatric literature. The articles are abstracted fully. It is always surprising how many articles have been missed during the course of a year's reading when this book appears as a reminder. Whether one considers himself a busy practitioner with all-too-little time for reading or really takes time to keep up with the current literature, this volume will be useful. It is, of course, a satisfactory way to maintain a permanent file of such articles in book form, year by year.

McCulloch.

# The Journal of Pediatrics

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## Original Communications

### HISTOPLASMIN SENSITIVITY

AMOS CHRISTIE, M.D., AND J. CYRIL PETERSON, M.D.  
NASHVILLE, TENN.

IN TWO previously reported studies<sup>1,2</sup> on the problems associated with the finding of pulmonary calcification in people insensitive to tuberculin, we were able to show that there is a remarkable correlation between histoplasmin sensitivity and calcified nodules in the lungs. This relationship was also reported by Palmer,<sup>3</sup> and his subsequent studies<sup>4</sup> have tended to elaborate and confirm this relationship. From our studies we thought that considerable significance could be attached to the age relationships in the development of sensitivity to tuberculin and histoplasmin and the age at which calcium deposits begin to appear in the chests of the children studied.

The early studies on the epidemiology of the unexplained calcifications, the data accumulating from our skin testing program, studies by Smith,<sup>5</sup> the studies of Palmer<sup>3,4</sup> and his associates, and the observations of the Williamson County Tuberculosis Study<sup>6</sup> have indicated considerable geographic variation in the prevalence of unexplained pulmonary calcifications and sensitivity to histoplasmin.

These studies have, of course, raised the question of how much significance can be attached to the finding of histoplasmin sensitivity.

Our experience, which now exceeds 2,000 histoplasmin tests in various age groups and from a considerable area of the country, is sufficient to enable us to add pertinent observations concerning the features of histoplasmin sensitivity.

#### STUDY MATERIAL

The children and young adults whom we have examined have been drawn from three groups:

Group I. A. 181 children, aged 2 to 19 years, from a child-caring institution in Williamson County, Tenn., the children chiefly originating from Middle Tennessee\* and

From the Department of Pediatrics, Vanderbilt University School of Medicine.  
Presented before the Meeting of the American Pediatric Society, Skytop, Pa., May 2, 1946.

\*Reported in detail.<sup>1</sup>

B. 315 children, aged 6 to 19 years, residents of the Tennessee Industrial School and having primary residence scattered over the whole of Tennessee.\*

Group II. 1,255 students at Vanderbilt University

A. 611 of whom were from Tennessee and

B. 644 from outside Tennessee

Group III. 381 patients tested at Vanderbilt University Hospital as in-patients and outpatients, chiefly residents of Middle Tennessee.

Groups I and II have been examined by chest roentgenograms, stereoscopic 4 by 5 inch films. Some of the children in Group III have had chest size, 7 foot, single films. All have been tested to histoplasmin† 0.001 c.c. and to 0.01 mg. or more of old tuberculin.

Individuals from Groups I and III were, in general, from the lower economic strata of their communities; Group II, on the other hand, was composed of college students and is more representative of the other economic extreme.

We have in these groups 1,488 children and young adults from Tennessee. In this group the age relationships of the phenomena of tuberculin sensitivity and histoplasmin sensitivity can be compared. As all children at Vanderbilt Hospital are not examined by x-ray, this group is excluded in the tabulations of pulmonary calcification. This leaves a group of 1,107 in which the age of the finding of pulmonary calcification by chest roentgenogram can be contrasted to the age relationship of tuberculin and histoplasmin sensitivity.

*The Concurrence of Histoplasmin Sensitivity and Pulmonary Calcifications.*—It is of interest at this point to diverge from our main thesis and to re-examine our over-all findings concerning the concurrence of histoplasmin sensitivity and pulmonary calcification. In Table I is shown the observed relationships between histoplasmin sensitivity and pulmonary calcification, and between the latter and tuberculin sensitivity.

TABLE I. NUMBER AND PER CENT SHOWING PULMONARY CALCIFICATIONS ACCORDING TO REACTIONS TO HISTOPLASMIN AND TUBERCULIN BY GROUPS

REACTION	RESIDENTS OF TENNESSEE									NONRESIDENTS		
	TOTAL			GROUP I			GROUP IIA			GROUP IIB		
	TOTAL	WITH CALCIUM		TOTAL	WITH CALCIUM		TOTAL	WITH CALCIUM		TOTAL	WITH CALCIUM	
		NO.	%		NO.	%		NO.	%		NO.	%
TOTAL	1,107	610	55.1	496	253	51.0	611	357	58.4	644	240	37.3
Histoplasmin +	168	99	58.9	91	58	63.7	77	41	53.2	34	23	67.6
Tuberculin +												
Histoplasmin +	701	434	61.9	273	161	59.0	428	273	63.8	181	93	51.4
Tuberculin -												
Histoplasmin -	38	16	42.1	21	9	42.8	17	7	41.2	70	28	40.0
Tuberculin +												
Histoplasmin -	200	61	30.5	111	25	22.5	89	36	40.4	359	96	26.7
Tuberculin -												

\*Reported in detail.<sup>2</sup>

†A positive reaction is 5 mm. or more of induration, and redness resulting from the intradermal injection of 0.001 ml. of filtrate of a broth culture of *Histoplasma capsulatum*. See Reference.<sup>1</sup>

In Table I, Group II has been subdivided into two classes, those residing within Tennessee and those whose primary residence is outside of the State. The total is for Tennessee residents and excludes those living outside of the State. Sixty-two per cent of the Tennessee residents who are sensitive to histoplasmin but not to tuberculin show pulmonary calcification, while only 42 per cent of those tuberculin-sensitive and histoplasmin-insensitive show pulmonary calcifications. A similar trend in difference is noted among the nonresidents of Tennessee who show 40 per cent calcifications among the tuberculin-sensitive histoplasmin-insensitive, and 51.4 per cent calcifications among the histoplasmin-sensitive tuberculin-insensitive individuals.

In Table II we have broken down the data on the skin reactions of the 610 individuals from Tennessee who showed pulmonary calcifications. It is apparent from this table that 87.4 per cent of those having pulmonary calcifications are sensitive to histoplasmin while only 18.8 per cent are tuberculin-sensitive.

TABLE II. HISTOPLASMIN AND TUBERCULIN REACTIONS IN 610 INDIVIDUALS FROM TENNESSEE HAVING PULMONARY CALCIFICATIONS

	NUMBER		PER CENT OF ALL INDIVIDUALS WITH CALCIFICATION	
Histoplasmin + Tuberculin +	99*		16.2	
Histoplasmin + Tuberculin -	434		71.1	
Subtotal Histoplasmin +		533		87.4
Tuberculin + Histoplasmin +	99*		16.2	
Tuberculin + Histoplasmin -	16		2.6	
Subtotal Tuberculin +		115		18.8
Histoplasmin - Tuberculin -		61		10.0

\*These individuals are duplicated to make subtotals correct.

In conjunction with the over-all correlation of histoplasmin sensitivity and pulmonary calcification, it is of interest to examine our data for the relationship to sensitivity and the degree of calcification. In Table III we have shown pulmonary calcifications divided into marked, i.e., multiple peripheral and hilar calcifications; moderate, i.e., single hilar and peripheral calcifications; and minimal, i.e., single hilar or peripheral lesions, both questionable and indubitable.

TABLE III. THE RELATIONSHIP OF THE DEGREE OF PULMONARY CALCIFICATION TO HISTOPLASMIN AND TUBERCULIN SENSITIVITY

TYPE OF SKIN REACTION	DEGREE OF CALCIFICATION										TOTAL	
	MARKED		MODERATE		MINIMAL		NONE		ALL WITH CALCIFI- CATION			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%		
Histoplasmin positive	96	86.1	419	79.8	135	62.2	434	48.2	650	76.4	1,084	61.9
Tuberculin positive	23	21.1	104	19.8	39	18.0	144	16.0	166	19.5	311	17.7
Histoplasmin and tuberculin negative	9	8.2	80	15.2	68	31.3	402	44.7	157	18.4	559	31.9
Total*	109		525		217		900		851		1,751	

\*As some individuals react to both antigens, the columns do not add up to the indicated totals.

Eighty-eight per cent of those with marked pulmonary calcifications were sensitive to histoplasmin; 62 per cent in the minimal calcification group were sensitive; and 48 per cent who showed no calcifications were positive. In the

tuberculin-sensitive group the corresponding percentages are 21, 18, and 16. It is also interesting to note that while only 9 of 109 with marked calcifications and 80 of 525 with moderate calcifications were insensitive to both histoplasmin and tuberculin, 402 of 900 who did not have calcifications failed to react to either antigen. This, of course, includes those too young to have developed calcifications and those who may have had calcifications and resolved them.

These findings confirm and elaborate the previous reports concerning the relationship of histoplasmin sensitivity to pulmonary calcifications.

*Age Distribution.*—In Table IV is shown the age distribution and the results of the histoplasmin tests in the various groups. In this table it is interesting to note that while only one child of 52 (1.9 per cent) reacted to histoplasmin the first year, in the second and third years there were 15 of 82 (18.3 per cent) who had developed sensitivity to the antigen. In the third and fourth years this rapid development of sensitization continues—23 of 63 (36.0 per cent) have become sensitized. The prevalence of sensitization then gradually increases with increased age until a maximum of 90 per cent is reached in the 21 through 22 year group.

TABLE IV. THE NUMBER TESTED AND PER CENT SHOWING POSITIVE REACTIONS TO HISTOPLASMIN BY AGE IN STUDY GROUPS

AGE	NUMBER TESTED				PER CENT POSITIVE			
	GROUP I	GROUP II	GROUP III	TOTAL	GROUP I	GROUP II	GROUP III	TOTAL
Under								
1 year	0	0	52	52	—	—	1.9	1.9
1-2	2	0	80	82	0.0	—	18.7	18.3
3-4	10	0	53	63	50.0	—	24.0	36.5
5-6	18	0	53	71	50.0	—	34.0	38.0
7-8	35	0	38	73	65.7	—	42.1	53.4
9-10	52	0	40	92	65.4	—	52.5	59.8
11-12	108	0	37	145	75.9	—	56.8	64.1
13-14	130	0	29	159	76.1	—	65.5	74.2
15-16	101	8	0	109	86.1	75.0	—	85.3
17-18	35	214	0	249	85.7	79.9	—	80.7
19-20	4	182	0	186	100.0	85.2	—	85.5
21-22	1	93	0	93	100.0	90.2	—	90.3
23-24	0	42	0	42	—	76.2	—	76.2
25-29	0	28	0	28	—	82.1	—	82.1
30 or more	0	45	0	45	—	77.8	—	77.8

Table V shows the results of tuberculin testing by age in the various groups.

The development of tuberculin sensitivity in these groups follows a quite different pattern from that observed concerning histoplasmin sensitivity. None of 52 children under 1 year of age were sensitive but in the group 1 through 2 years of age there were 5 of 82 (6.1 per cent) positive. There was then a slow increase in the prevalence of sensitization in the low economic class represented by Group I until a maximum of 15 of 35 (42.8 per cent) was reached in the age group 17 through 18 years. At this point the classes shift and young adults from the high economic plane represented by the university students become the greatly predominant group. It is interesting to note that in this group for the same age, 17 through 18 years, only 27 of 214 (12.6 per cent) are tuberculin-sensitive.

TABLE V. NUMBER TESTED AND PER CENT SHOWING POSITIVE REACTIONS TO TUBERCULIN BY AGE AND BY GROUP

AGE	NUMBER TESTED				PER CENT POSITIVE			
	GROUP I	GROUP II	GROUP III	TOTAL	GROUP I	GROUP II	GROUP III	TOTAL
Under 1 year	0	0	52	52	-	-	0.0	0.0
1-2	2	0	80	82	0.0	-	6.2	6.1
3-4	10	0	53	63	0.0	-	3.8	3.2
5-6	18	0	53	71	11.1	-	11.3	11.3
7-8	35	0	38	73	17.1	-	10.5	13.7
9-10	52	0	40	92	3.8	-	25.0	13.0
11-12	108	0	37	145	23.1	-	18.9	22.0
13-14	130	0	29	159	23.8	-	27.6	24.5
15-16	101	8	0	109	30.7	0.0	-	28.4
17-18	35	214	0	249	42.8	12.6	-	16.8*
19-20	4	182	0	186	0.0	13.2	-	12.9
21-22	1	93	0	93	0.0	17.4	-	17.2
23-24	0	42	0	42	-	19.0	-	19.0
25-29	0	28	0	28	-	23.0	-	25.0
30 or more	0	45	0	45	-	26.7	-	26.7

\*At this point the group balance shifts from the low economic levels represented by Groups I and III to the high economic level represented by Group II, college students.

In Table VI is shown the development of pulmonary calcification by age in Groups I and II.

The development of pulmonary calcification, while not observed in the children less than 5 years of age, increased very sharply from this period to attain a level of 57.7 in the group 9 through 10 years. From this period on the acquisition of pulmonary calcification is very gradual, reaching a maximum level of 66.7 per cent in the 19 through 20-year group, and with a tendency to fall off in the older age groups.

TABLE VI. THE NUMBER X-RAYED AND PER CENT SHOWING CALCIFICATIONS BY AGE IN GROUPS I AND II

AGE	NUMBER X-RAYED			PER CENT WITH CALCIFICATION		
	GROUP I	GROUP II	TOTAL	GROUP I	GROUP II	TOTAL
Under 1 year	0	0	0	-	-	-
1-2	0	0	2	0.0	-	0.0
3-4	10	0	10	0.0	-	0.0*
5-6	18	0	18	16.7	-	16.7
7-8	35	0	35	42.8	-	42.8
9-10	52	0	52	57.7	-	57.7
11-12	108	0	108	50.0	-	50.0
13-14	130	0	130	58.5	-	58.5
15-16	101	8	109	51.2	75.0	53.2
17-18	35	214	249	51.4	59.8	58.6
19-20	4	182	186	100.0	65.9	66.7
21-22	1	92	93	100.0	44.6	45.2
23-24	0	42	42	-	50.0	50.0
25-29	0	28	28	-	71.4	71.4
30 or more	0	45	45	-	46.7	46.7

\*Though not tabulated because of incomplete observations, roentgenograms of Group III also show absence of calcification in the youngest age groups.

The relationships of these observations can be more easily seen in graphic representation. In Chart 1 are shown the curves for the development of pulmonary calcification, tuberculin sensitivity, and histoplasmin sensitivity for all



groups except in the calcification curves where Group III is omitted because of incomplete observation.

This Chart brings out strikingly the fact that in the 17 through 18-year group the prevalence of tuberculosis as measured by tuberculin tests is three times as high in children from the lower economic group as contrasted to university students.

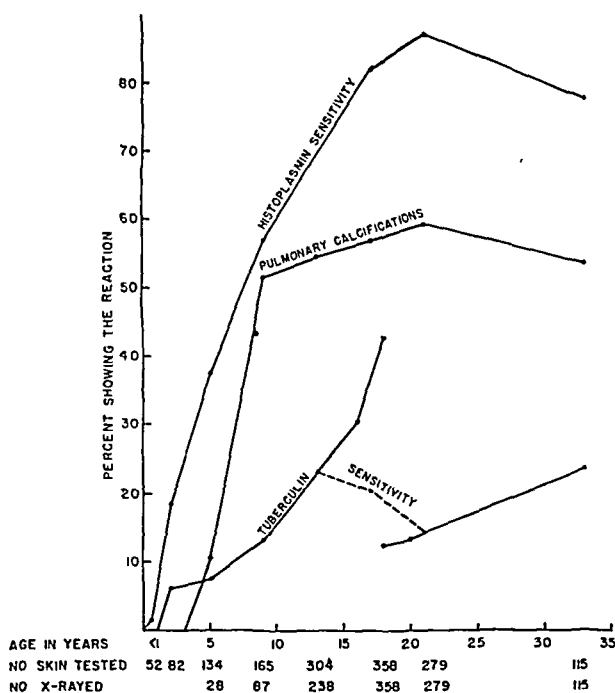


Chart 1.—Age relationship in the development of histoplasmin sensitivity, pulmonary calcification, and tuberculin sensitivity.

More pertinent to this study is the relationship of the curves for the development of histoplasmin sensitivity and pulmonary calcification. Here it is apparent that while there is a considerable lag in the development of pulmonary calcification as compared with histoplasmin sensitivity their relationship is such that the pulmonary calcification could follow and be related to the development of the histoplasmin sensitivity. This is of greater significance in view of the findings in our previous studies and those of Palmer<sup>3</sup> which show a high degree of correlation between the presence of histoplasmin sensitivity and pulmonary calcification.

It is also of interest to note that while there is a coincidence of the peak of histoplasmin sensitivity and pulmonary calcification, the same is not true for tuberculin sensitivity. It is also of considerable significance that the peak and depression of tuberculin sensitivity found by superimposing the groups of differing economic status is in no way reflected in the curve of pulmonary calcification. This in itself seems to indicate that there is a more intimate relationship

between the presence of histoplasmin sensitivity and pulmonary calcification than between this latter phenomenon and tuberculin sensitivity, at least in the groups observed.

Another point of interest concerning the relationship of these observations is the fact that early pulmonary calcification follows histoplasmin sensitivity more intimately than is the case in the ages beyond puberty. This point will be subjected to analysis later.

*Geographical Distribution.*—The examination of the geographical pattern of sensitivity distribution and pulmonary calcification is of interest not only because it gives some indication of the relative presence or absence of infection in a given area, but also because the fluctuations in different areas aid in examining the relationship of the phenomena, and finally because the variations are of value in assessing the significance of the histoplasmin test.

Among the children and young adults of Groups I and II we have 926 persons from the State of Tennessee and 644 from outside the State but principally from states in the southeastern section of the United States and from Pennsylvania, New Jersey, and New York.

In Table VII is shown the distribution of histoplasmin and tuberculin sensitivity and pulmonary calcifications of Groups I and IIA, aged 2 through 30 years, by six arbitrary divisions of the State of Tennessee. In some divisions the numbers are not large but in all they are enough to indicate the general pattern of the reactions. In this table it is readily apparent that pulmonary calcifications vary in each segment directly with the histoplasmin sensitivity. The eastern sections of the State with low prevalence of histoplasmin sensitivity also show the lowest prevalence of pulmonary calcifications. On the other hand the East East section with the lowest incidence of pulmonary calcifications was in tuberculin sensitivity next to the East West segment where the highest prevalence of both tuberculin sensitivity and pulmonary calcifications was observed. Also, there is in every section much more calcification than can be explained on the basis of tuberculous infections as indicated by the tuberculin test. In general, there was a less direct relationship between the relative levels of tuberculin sensitivity and pulmonary calcifications than between the latter and histoplasmin sensitivity.

TABLE VII. NUMBER AND PER CENT OF PERSONS FROM TENNESSEE SHOWING PULMONARY CALCIFICATIONS, HISTOPLASMIN SENSITIVITY AND TUBERCULIN SENSITIVITY ACCORDING TO THEIR RESIDENCE IN SIX SECTIONS OF THE STATE

SECTIONS OF TENNESSEE	TOTAL	HISTOPLASMIN		CALCIFICATION		TUBERCULIN	
		NO. POS.	% POS.	NO. POS.	% POS.	NO. POS.	% POS.
TOTAL	926	737	79.6	531	57.3	161	17.4
East East	74	31	41.9	20	27.0	16	21.6
West East	50	25	50.0	16	32.0	5	10.0
East Middle	41	32	78.0	19	46.3	7	17.1
West Middle	626	536	85.6	389	62.1	105	16.8
East West	33	27	81.8	23	69.7	9	27.3
West West	101	86	85.1	63	62.4	19	18.8
Unknown	1			1			

In Charts 2 and 3 are shown the sectional distribution for Tennessee of histoplasmin sensitivity and pulmonary calcifications, respectively. Here it is graphically demonstrated that there is a close association between histoplasmin sensitivity and pulmonary calcification.

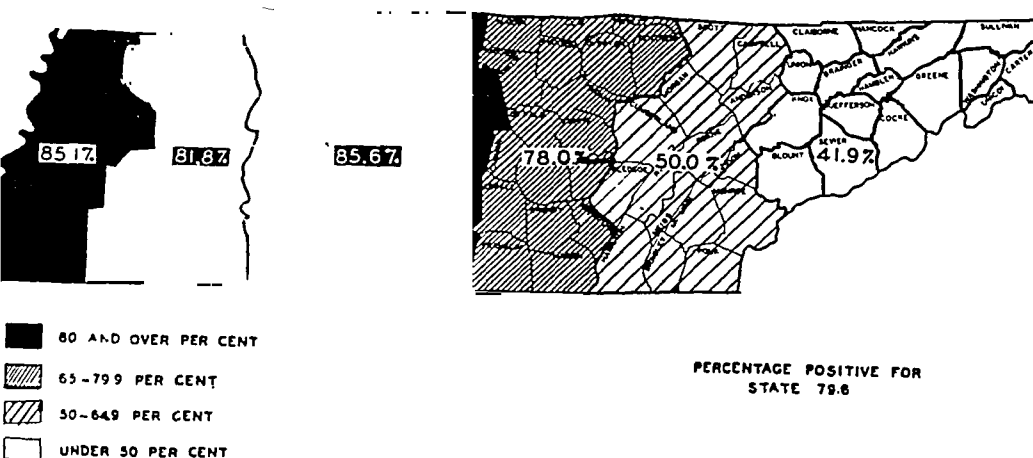


Chart 2.—Percentage of persons (by county of residence, 1945) examined at Vanderbilt University and Tennessee Industrial School who reacted to histoplasmin.

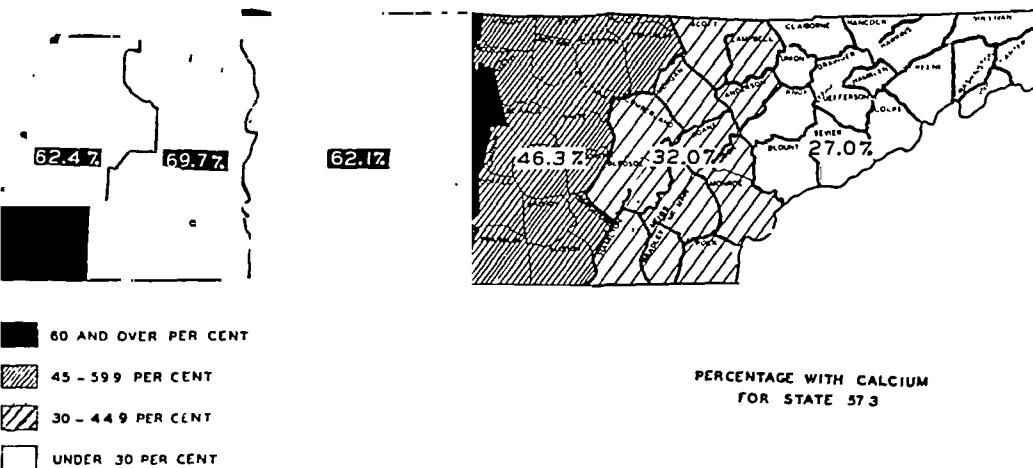


Chart 3.—Percentage of persons (by county of residence, 1945) examined at Vanderbilt University and Tennessee Industrial School who were found to have calcification.

In Table VIII and Charts 4 and 5 is shown the geographical distribution of sensitivity to histoplasmin and tuberculin and of pulmonary calcifications in the people of Group II. Group I is omitted because it does not represent a comparable age group.

The fact that most of the people come from states adjacent to Tennessee which are areas with a high incidence of histoplasmin sensitivity makes the

TABLE VIII. NUMBER AND PER CENT OF PERSONS AT VANDERBILT UNIVERSITY HAVING PULMONARY CALCIFICATIONS, HISTOPLASMIN SENSITIVITY AND TUBERCULIN SENSITIVITY ACCORDING TO STATE OF PRIMARY RESIDENCE

STATE	TOTAL	HISTOPLASMIN-POSITIVE		CALCIFICATION ON X-RAY		TUBERCULIN-POSITIVE	
		NO.	%	NO.	%	NO.	%
TOTAL	1255	720	57.4	597	47.6	198	15.8
Alabama	77	36	46.8	27	35.1	12	15.6
Arizona	1	0	—	0	—	0	—
Arkansas	19	9	47.4	7	36.8	2	10.5
California	5	1	*	0	—	1	*
Colorado	1	0	—	0	—	1	*
Connecticut	4	3	*	0	—	0	—
District of Columbia	2	0	—	1	*	0	—
Florida	30	6	20.0	10	33.3	3	10.0
Georgia	43	5	11.6	11	25.6	0	—
Illinois	13	3	23.1	6	46.2	1	7.7
Indiana	11	6	54.5	4	36.4	4	36.4
Iowa	1	0	—	0	—	0	—
Kansas	2	1	*	0	—	0	—
Kentucky	56	47	83.9	36	64.3	13	23.2
Louisiana	11	4	36.4	6	54.5	0	—
Maryland	3	1	*	1	*	0	—
Massachusetts	2	0	—	0	—	0	—
Michigan	6	1	*	3	*	1	*
Minnesota	1	0	—	0	—	0	—
Mississippi	32	19	59.4	18	56.2	3	9.4
Missouri	11	8	72.7	7	63.6	4	36.4
New Hampshire	1	0	—	0	—	0	—
New Jersey	61	5	8.2	19	31.1	17	27.9
New Mexico	1	0	—	0	—	0	—
New York	76	8	10.5	21	27.6	13	17.1
North Carolina	12	4	33.3	4	33.3	3	25.0
Ohio	9	5	*	7	*	0	—
Oklahoma	9	4	*	3	*	1	*
Oregon	1	1	*	1	*	0	—
Pennsylvania	39	8	20.5	14	35.9	8	23.1
South Carolina	27	4	14.8	4	14.8	4	14.8
Tennessee	611	505	82.6	357	58.4	94	15.4
Texas	27	7	25.9	4	14.8	4	14.8
Virginia	15	5	32.3	6	40.0	1	6.7
Washington	1	0	—	1	*	0	—
West Virginia	14	3	21.4	6	42.9	3	21.4
Wisconsin	2	0	—	1	*	1	*
Wyoming	1	0	—	0	—	0	—
Out of country	4	2	*	1	*	2	*
Unknown	13	9	69.2	11	84.6	1	—

\*Percentages not calculated for states with less than ten examined.

over-all histoplasmin sensitivity high. In general, it may be seen that the percentage of histoplasmin reactors is higher in the states of the Western Appalachian slope and those just west of the Mississippi River. The states having the highest prevalence of histoplasmin sensitivity have, in general, the highest incidence of pulmonary calcifications. The numbers of individuals tested in the states outside of Tennessee are usually so low that little more than tendencies can be shown.

The relationship of pulmonary calcifications to tuberculin sensitivity is not as regularly apparent.

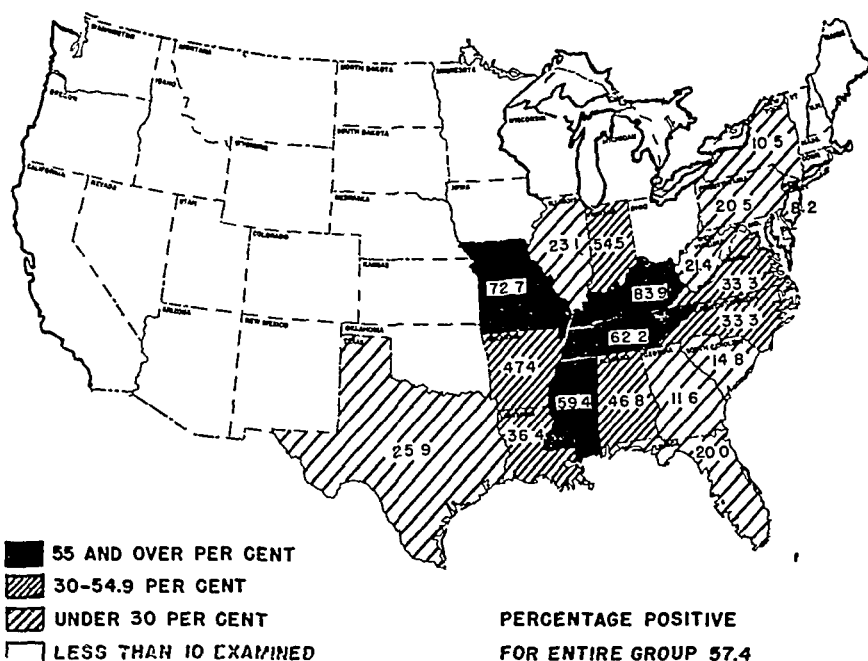


Chart 4—Distribution by state of residence of the percentage of persons who were examined at Vanderbilt University in 1945, and found to react to histoplasmin

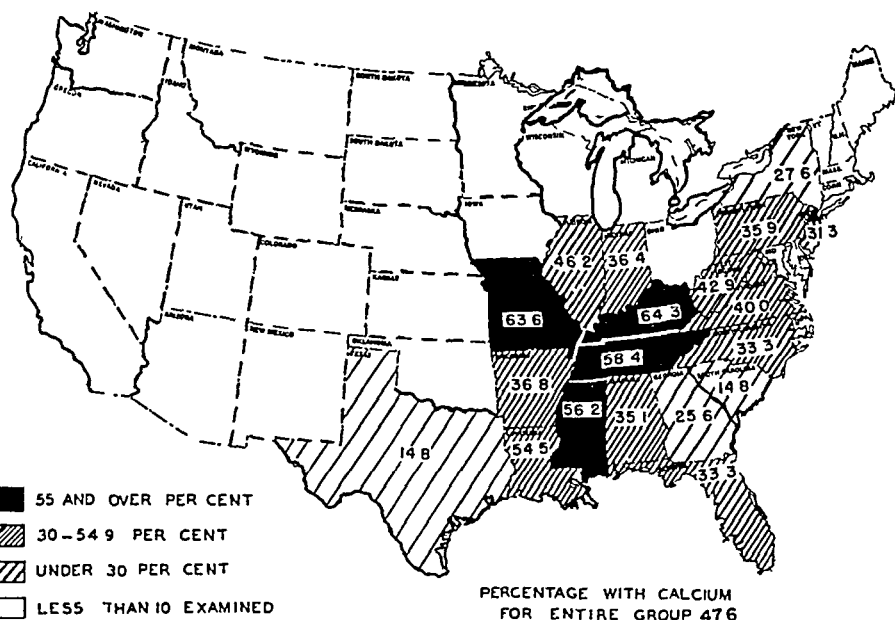


Chart 5—Distribution by state of residence of the percentage of persons who were examined at Vanderbilt University in 1945 and found to have calcification

In Table IX we have set up two groups for contrast. Students from states other than Tennessee<sup>\*</sup> with more than 10 individuals having less than 25 per cent sensitivity to histoplasmin are contrasted with those having more than 25 per cent histoplasmin sensitivity. The sensitivity to tuberculin and histoplasmin and the calcification by degrees of calcification as well as the total are shown. From this table it may be seen that while there is a 65 per cent higher incidence of tuberculin sensitivity among the students from the states of low histoplasmin sensitivity, there is among these students only 65 per cent as much pulmonary calcification as in the states with high histoplasmin sensitivity. Furthermore, the pulmonary calcifications in those students from low histoplasmin-sensitivity areas are 48 per cent of the minimal degree and only 2 per cent of the marked degree, while those from high histoplasmin-sensitivity areas show only 22 per cent minimal calcifications, 65 per cent moderate calcifications, and 13 per cent marked calcifications.

TABLE IX. THE CONTRAST OF TUBERCULIN SENSITIVITY, HISTOPLASMIN SENSITIVITY AND PULMONARY CALCIFICATIONS IN GROUPS OF STATES HAVING LOW AND HIGH PREVALENCE OF HISTOPLASMIN SENSITIVITY

	NUMBER OF IN- DIVID- UALS	CALCIFICATION								HISTO- PLASMIN POSITIVE		TUBER- CULIN POSITIVE	
		TOTAL		DEGREE									
				1		2		3					
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
States with low prevalence of histoplasmin sensitivity*	303	91	30.0	44	48.3	45	49.4	2	2.2	45	14.8	59	16.5
States with high prevalence of histoplasmin sensitivity†	262	119	45.4	26	21.8	77	64.7	16	13.4	82	31.3	26	9.9

\*Florida, Georgia, Illinois, New Jersey, New York, Pennsylvania, South Carolina, West Virginia.

†Alabama, Arkansas, Indiana, Kentucky, Louisiana, Mississippi, Missouri, North Carolina, Texas, and Virginia.

*The Significance of Histoplasmin Sensitivity.*—From the studies to date it is apparent that a positive histoplasmin test even in fairly young individuals cannot have great significance as an indicator of active disease. In children, 4 through 5 years old, 50 per cent have become sensitized and are without any evidence of a clinically significant infection. The value it might have as an exclusion test is clouded because most of the patients with advanced proved histoplasmosis who have been tested have been found negative. Parsons and Zarafonitis,<sup>7</sup> Davis and Neff,<sup>8</sup> and McLeod, Emmons, Ross, and Burke,<sup>9</sup> have reported patients with miliary histoplasmosis who failed to react to histoplasmin. We are also acquainted with another case in a patient of Crosswell<sup>10</sup> who failed to react to histoplasmin. While the failure may have been due to the use of inadequate dilutions of outdated antigen in the case of Parsons and Zarafonitis, as they suggested, the same is not true in the other cases where known potent histoplasmin was used. Our interest in the test resulted in part from a positive

\*Florida, Georgia, Illinois, New Jersey, New York, Pennsylvania, South Carolina, West Virginia.

†Alabama, Arkansas, Indiana, Kentucky, Louisiana, Mississippi, Missouri, North Carolina, Texas, and Virginia.

response obtained in a 5-month-old infant who was dying with histoplasma sepsis, an instance where one might have expected to have found an exhaustion anergy. It is of some interest to note that all the parents of the last five patients mentioned reacted strongly to histoplasmin. It is probable that the test, like the tuberculin test, is satisfactory as an exclusion test in the mild acute, subacute, and chronic forms of the infection. It would seem quite probable that less sensitivity might exist during a time when the infection is very active, comparable to the anergy seen in tuberculin testing during miliary infections. It is suggested under such circumstances that tests with a series of dilutions be used, through to the 1:10 dilution with presently available preparations.

The recent studies of Emmons, Olson, and Ethridge<sup>11</sup> have cast considerable doubt upon the specificity of the histoplasmin test. They have shown that histoplasmin reacts almost invariably in animals experimentally infected with *Blastomyces dermatitidis* or *Haplosporangium parvum* and much less frequently in experimental infections with *Coccidioides immitis*. On the other hand, blastomycin and coccidioidin reacted much less commonly in a nonspecific manner; the blastomycin reacted with only 17 of 39 animals infected with *H. capsulatum*, with none of 7 infected with *C. immitis* and with 6 of 7 infected with *Haplosporangium parvum*.

From these observations one might say that histoplasmin gave frequent non-specific reactions; that it may well serve as an index of sensitization to various fungi. It has been stated in previous studies<sup>1, 2, 3</sup> that such a situation might exist; that the histoplasmin sensitivity may be indicative of more than *H. capsulatum* infection; that it might be indicative of sensitization by some agent having an antigenic complex closely related to that of histoplasmin.

In one of our studies<sup>1</sup> we have reported on the responses of 125 children and young adults of Tennessee to coccidioidin. While there were many in the group who reacted to histoplasmin, there was not one who gave a clear-cut positive reaction to coccidioidin. Similarly in another group tested to histoplasmin<sup>2</sup> we carried out simultaneous skin tests with haplosporangin. In the group of over 300 so tested there were only two doubtful reactions, none acceptably positive.

As far as these findings go they were in general agreement with those of Emmons<sup>11</sup> as his study showed haplosporangin reacting very specifically and coccidioidin reacting only once in 39 animals infected with *H. capsulatum*, once in 8 animals infected with *B. dermatitidis*, and in 4 of 7 animals infected with *Haplosporangium parvum*. It would seem, however, that there is less tendency for cross-reactions to occur in children and young adults than in experimental animals as judged by the failure to get any false reactions with coccidioidin.

The failure to find many young infants sensitive to histoplasmin would make it seem very unlikely that infection with *Candida albicans* can be of real significance in relationship to histoplasmin sensitivity. Oral thrush is a common infection of infants in this section and would, if it produced cross-sensitivity reactions, be likely to yield a high percentage of infantile reactors. Furthermore, thrush is not a commonly recognized infection among the children of the age groups where we commonly see histoplasmin sensitivity.

There is certainly need for further study, in groups such as we have studied, of sensitization to the antigens derived from other fungi responsible for systemic mycoses. The study of Emmons<sup>11</sup> showed that there was a marked mutual crossing of the reactions to histoplasmin and blastomycin in experimentally infected animals and in patients with chronic pulmonary disease. This would clearly indicate a need for further study of the cross-reactions of these antigens and also the need to examine clinical material for the possibility of unrecognized mild forms of blastomycosis.

Our studies yield information which makes it seem quite certain that the reactions observed are truly allergic phenomena, reactions to some antecedent infection, rather than being simple reactions to nonspecific irritants contained in the preparation.

In regard to this, the pattern of age response is such as one would expect from a widely disseminated infectious agent. Sensitization occurs only very rarely in early infancy. *The only positive reaction we have encountered in a child less than 6 months of age was in an infant dying with proved histoplasmosis and we have seen only one other positive reaction in an infant less than 1 year of age.* The rapid increase in sensitization in the next few years of life is certainly not correlated with any particular developmental achievement. It is rather like the development of Schick negativens in the non-immunized urban groups, a phenomenon no longer generally believed to be due to normal development but generally attributed to immunizations resulting from subclinical infections, the clinical horizon for which might be lowered by improvement in clinical perception or the development and wider use of improved laboratory techniques in demonstrating the infection.

The character of the responses obtained might be cited; in the young the reactions tend to be ++ and +++ in a high proportion of the cases, while in older age groups + reactions are more frequent. This may be interpreted as suggesting that the reaction is more vigorous when first developed but tends to become attenuated after a time, even where reinfection occurs to maintain the reaction. A similar phenomenon is observed in tuberculous infection where "epituberculosis" or massive benign perifocal allergic reaction with its extreme sensitization, generally as well as locally, is a peculiarity of early childhood infection.

The geographical distributions of histoplasmin sensitivity also offer strong support for the supposition that the reaction is a response to an infectious process. Our studies showing the geographical pattern of sensitivity to histoplasmin are unfortunately, to date, entirely in the older children and young adults.

These studies, however, show that there is a wide variation in the incidence of sensitivity from one area to another within the State of Tennessee. Indeed, the extensive studies reported by Palmer<sup>4</sup> showed that there was in other states a similar variability and that this variability in states bordering the areas of high prevalence of sensitivity was integrated with the geographical relationship of the state to the bordering areas of high prevalence of



sensitivity. If we assume, as seems apparent, that the center of this infection is in Kentucky and Missouri, our findings in the State of Tennessee show a similar gradation.

Furthermore, the wide variation in sensitivity observed in our studies in students from different states, and in the studies of Palmer<sup>3, 4</sup> shows that the variation is in relationship to a fairly definite geographical focus and is suggestive of an infectious agent existing commonly in an area where climatic factors favor its propagation. A similar relationship has been recognized in the problem of coccidioidomycosis, an infection in which sharply delimited foci of propagation and infection have been demonstrated.

In California, Smith<sup>5</sup> has observed that there is almost a complete absence of reactions to histoplasmin, and that those native Californians who do react are also reactors to coccidioidin and have presumably had coccidioidomycosis.

Finally, there is the relationship of histoplasmin sensitivity to pulmonary calcification, a demonstrable pathologic lesion. Our studies show that 76 per cent of the whole group who have pulmonary calcifications react to histoplasmin inclusive of all age groups, while only 48 per cent of those not showing calcifications have been sensitized to the antigen, again inclusive of the younger age groups who might subsequently develop calcifications. These differences are so great that one must accept the fact that they are positively associated.

None of these studies prove a direct causal relationship between pulmonary calcifications and histoplasmosis. The histoplasmin sensitivity may merely be an index of the over-all problem of pulmonary and systemic mycotic infections. Further studies of the problem of cross-sensitivity among fungus antigens and infections are needed. Further study to establish the exact etiologic agent or agents responsible for the histoplasmin sensitivity and pulmonary calcifications are imperative.

#### DISCUSSION

In Chart 1 there was observed a marked divergence of the curves of histoplasmin sensitivity and the development of pulmonary calcifications beginning at the 9-year level as charted but which actually develop at about 11 years. This divergence may be due to the interaction of several possible factors, none of which has yet been studied. It is apparent from the observations as a whole that there is a lessened prevalence of sensitivity to histoplasmin and of pulmonary calcification in the older age groups. It would seem quite possible that small lesions may evolve, through calcification and resorption, at a rate greater than the rate of loss of histoplasmin sensitivity, that the calcification of a given lesion might be resorbed before loss of histoplasmin sensitivity occurs. It is also possible that in the postpubescent groups calcification of a given lesion is less likely to occur. It is furthermore possible that repeated stimuli may maintain histoplasmin sensitivity without producing lesions which go on to calcification.

If the suggestive finding of a lessened prevalence of histoplasmin sensitivity in the older groups is substantiated it may also suggest the manner in

which the infection is acquired. It could indicate that older age groups with their more restrained mode of living and less likelihood of intimate contact with the soil are less likely to come into contact with the infectious agent. Also of significance in relationship to this are observations made by the Williamson County Tuberculosis Study<sup>6</sup> group showing that among the strictly rural groups this tendency to falling off of histoplasmin sensitivity in the older age groups is not observed; suggesting that among people who live closer to nature, i.e., the soil, the sensitivity is maintained throughout life.

The age at which sensitivity develops, its absence in the first year of life, is also suggestive that the infection is not a household contagion and that the fungus is not commonly transmitted from one individual to another. The rapid acquisition of sensitization after the child is able to get out and about again points to a source intimate to the soil. If the soil be the source of the fungus, then it is probable that the acquisition of sensitization would occur earlier in rural as contrasted to urban groups. This observation also indicates the need for study of the details of physical geography in relation to sensitization.

These studies seem to have definite significance from the viewpoint of the interpretations of the mass roentgenographic studies now being made and contemplated.

It seems quite certain that in states bordering the western bank of the Mississippi River and the states of the Western Appalachian slope a large part of the pulmonary calcifications are due to some infection other than tuberculosis. It seems that while this relationship is most striking in that area, it is not confined to this area but has a much wider application. Our studies showing levels of sensitivity of 10 to 20 per cent even in the states outside of the high-prevalence area and those of Palmer<sup>4</sup> would suggest that pulmonary calcifications due to mycotic infection are not limited to the western area of coccidioidomycosis and the eastern Mississippi Valley area of high histoplasmin sensitivity.

Personal communications from a number of Army surgeons would seem to indicate that the problem of men developing pulmonary calcifications while in the Service is one which is causing considerable difficulties in the discharge of Army personnel. Routine discharge roentgenograms are bringing out the fact that there are numbers of men who have developed pulmonary calcifications which presumably were not present at the time of induction.

It is also true that many men were classified as 4-F on the basis of having pulmonary calcifications either too numerous or too large to pass military standards. It would seem from these studies that the majority of these were probably not due to tuberculous infection but rather to a benign pulmonary mycosis, already healed beyond reasonably probable breakdown.

If these studies have no other value, they do serve to reinstitute and re-emphasize the necessity of employing tuberculin tests or the demonstration of tubercle bacilli in establishing the diagnosis of tuberculosis in minimal and noncavitated pulmonary lesions and in the healing lesions with pulmonary calcifications.

## SUMMARY

1. The subject of the concurrence of pulmonary calcification and histoplasmin sensitivity is reviewed and the accumulated observations concerning this are presented.

2. The age relationships in the development of histoplasmin sensitivity, pulmonary calcifications, and tuberculin sensitivity have been presented.

3. The geographical variations of histoplasmin sensitivity, pulmonary calcifications, and tuberculin sensitivity in more than 1,000 children and young adults resident in Tennessee are shown.

4. The geographic variations in histoplasmin sensitivity, pulmonary calcifications, and tuberculin sensitivity as demonstrated by 611 college students residents of Tennessee and 644 college students residents of various states of southeastern United States and Pennsylvania, New Jersey, and New York have been shown.

5. The significance of histoplasmin sensitivity as demonstrated in these studies has been discussed.

6. The significance of these studies in relationship to the study of the epidemiology of tuberculosis is discussed.

We are greatly indebted to members of the Williamson County Tuberculosis Study and to the Tennessee State Health Department, particularly to Dr. Ruth Puffer, who gave us valuable assistance in the tabulations and statistical analysis of the material; to Drs. R. S. Gass and E. F. Harrison, who read the roentgenograms and made many pertinent and useful comments on the study; and to Commissioner R. H. Hutcheson for his general aid and encouragement.

We are also indebted to the staff of the Vanderbilt University Student Health Service, particularly to Dr. Tom Zerfoss and Dr. Alvin Keller, who made it possible for us to include observations on Group II in our study.

## REFERENCES

1. Christie, A., and Peterson, J. C.: *Am. J. Public Health* 35: 1131, 1945.
2. Christie, A., and Peterson, J. C.: The Relationship of Sensitivity to Histoplasmin, Tuberculin, and Haplosporangin to Pulmonary Calcification, *J. A. M. A.* 131: 658, 1946.
3. Palmer, C. E.: *Pub. Health Rep.* 60: 513, 1945.
4. Palmer, C. E.: *Pub. Health Rep.* 61: 475, 1946.
5. Smith, Charles E., Stanford University: Personal communications.
6. Williamson County Tuberculosis Study: Unpublished data.
7. Parsons, B. J., and Zarafonetis, C. J. D.: *Arch. Int. Med.* 75: 1, 1945.
8. Davis, H. V., and Neff, F. C.: *Am. J. Dis. Child.* 71: 171, 1946.
9. McLeod, J. H., Emmons, C. W., Ross, S., and Burke, F. G.: *J. PEDIAT.* 28: 275, 1946.
10. Crosswell, C., 1145 Madison Avenue, Memphis: Personal communication.
11. Emmons, C. W., Olson, B. J., and Eldridge, W. W.: *Pub. Health Rep.* 60: 1383, 1945.

# ELECTROPHORETIC PATTERNS OF BLOOD SERA IN POLIOMYELITIS AND GUILLAIN-BARRÉ'S DISEASE (ENCEPHALOMYELORADICULITIS)

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NORMAL blood sera and plasmas have been carefully studied electrophoretically by Longsworth, Shedlovsky, and MacInnes,<sup>1</sup> Seudder,<sup>2</sup> Moore and Lynn,<sup>3</sup> and by Dole.<sup>4</sup> These investigators have reported the normal composition of the serum and plasma proteins and the relative amounts of the electrophoretic fractions (albumin, alpha globulin, beta globulin, gamma globulin, and fibrinogen) present.

Tiselius<sup>5</sup> first determined the order of migration of the protein fractions of plasma. He used horse serum buffered at pH 7.7 and found the order of migration to be albumin, alpha globulin, beta globulin, fibrinogen, and gamma globulin. Stenhagen<sup>6</sup> then showed that a similar order of migration held true in human plasma.

In the diagrams obtained for the descending boundary in the U-shaped electrophoresis tube a disturbance is commonly observed in the beta globulin boundary, showing up as a very narrow and sharp peak. The cause of this beta disturbance is as yet unknown. Dole<sup>7</sup> states that 14 of 15 normal subjects showed this beta disturbance, and the fifteenth showed it on repetition. Furthermore, one subject showed the beta disturbance on 19 of 20 runs, the one exception being when the blood was not drawn as a fasting sample.

Numerous reports of characteristic changes<sup>1, 8-12</sup> in the electrophoretic patterns of the blood sera in various pathologic conditions have appeared in the recent medical literature. However, in so far as we have been able to determine, there have been no data published on the electrophoretic patterns of sera from cases of poliomyelitis or of Guillain-Barré's disease (encephalomyeloradiculitis). It seemed possible that a study of the sera of cases of these diseases might reveal some characteristic changes in the electrophoretic patterns. The present study was undertaken to determine whether such changes could be demonstrated.

## METHODS

The sera investigated were taken, with a few exceptions, from patients in the Department of Pediatrics of the University of Minnesota Hospitals. The blood specimens drawn were all morning, fasting specimens.

The sera were dialyzed for three days at a temperature of 4° C. against a phosphate buffer of pH 7.65 and ionic strength of 0.1, the buffer being changed each day and the final dialysis being made against the total volume of buffer

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DETEC- MINATION NUMBER	NAME	AGE	SEX	DIAGNOSIS	DAYS AFTER ONSET	CHANGE IN BETA DISTURB- ANCE	SPLIT OF ALBUMIN PEAK	ELEVATION OF INTER- PHASE	pH	PARALYSIS
1	M. D.	9	M	Normal*	-	0	±	-	7.65	None
2	J. R.	5	M	Normal†	-	0	-	-	7.65	None
3	M. Z.	15	F	Normal†	-	0	-	-	7.65	None
24	R. S.	9	M	Normal†	-	0	-	-	8.0	None
41	J. O.	6	F	A. A. P. §	6	1+	±	-	7.65	Slight
10	A. G.	4	F	A. A. P.	8	2+	-	+	7.65	Moderate
36	G. P.	8	M	A. A. P.	8	0	±	-	7.65	Slight
4	M. T.	11	F	A. A. P.	10	2+	±	+	7.65	Slight
37	R. S.	9	M	A. A. P.	10	3+	-	+	7.65	None
38	J. R.	12	M	A. A. P.	11	2+	+	+	7.65	None
39	R. R.	8	M	A. A. P.	11	3+	-	+	7.65	None
5	D. L.	5	M	A. A. P.	14	2+	+	+	7.65	Moderate
40	G. P.	8	M	A. A. P.	19	1+	+	+	7.65	Slight
9	J. B.	9	M	A. A. P.	26	2+	-	+	7.65	Moderate
7	L. L.	4	M	A. A. P.	51	2+	+	-	7.65	Moderate
6	V. B.	15	M	A. A. P.	54	1+	+	-	7.65	Moderate
17	J. P.	6	M	A. A. P.	100	2+	+	-	8.0	Slight
25	M. T.	11	F	A. A. P.	107	1+	-	+	7.65	Severe
16	H. D.	13	M	A. A. P.	113	3+	+	+	7.65	Severe
15	M. N.	14	F	A. A. P.	119	3+	+	+	7.65	Moderate
30	D. L.	5	M	A. A. P.	238	3+	+	+	7.65	Severe
34	J. Z.	19	F	A. A. P.	238	3+	±	+	7.65	Severe
31	P. M.	9	F	A. A. P.	238	1+	±	+	7.65	Moderate
18	E. J.	14	F	A. A. P.	260	0	±	-	7.65	Severe
33	H. S.	23	F	A. A. P.	300	2+	+	+	7.65	Severe
11	S. C.	21	M	A. A. P.	11 mo.	3+	-	+	7.65	Severe
32	D. A.	4	F	A. A. P.	40 mo.	1+	+	+	7.65	Severe
21	J. K.	19	F	A. A. P.	14 yr.	2+	±	-	7.65	Slight
12	B. W.	25	M	A. A. P.	18 yr.	3+	±	+	7.65	Severe
28	J. S.	24	M	A. A. P.	22 yr.	1+	+	-	7.65	Severe
43	T. H.	42	M	Guillain-Barré	11	1+	+	-	7.65	Severe
42	J. K.	13	M	Guillain-Barré	60	1+	+	-	7.65	Severe
35	D. G.	39	M	Guillain-Barré	75	2+	-	-	7.65	Severe
8	G. C.	9	M	Guillain-Barré	223	1+	+	-	7.65	Severe
29	R. M.	24	M	Guillain-Barré	18 mo.	1+	+	+	7.65	Slight
26	M. P.	15	F	Paralysis of unknown etiology	137	0	-	-	7.65	Severe
27	G. M.	12	M	Pseudohypertrophic progressive muscular dystrophy	9 yr.	0	-	-	7.65	Severe weakness

\*Stenosis of larynx.

†Fracture of femur.

required to fill the electrode chambers of the electrophoresis cell. At the end of dialysis the sera were cleared by centrifugation and diluted with three volumes of the buffer against which they had been dialyzed.

The electrophoretic patterns of these diluted sera were then obtained after 9,000 seconds of electrophoresis under a potential gradient of 5.33 volts per centimeter by the "schlieren scanning" method of Longworth.<sup>13</sup>

#### EXPERIMENTAL

The cases studied included 23 cases of poliomyelitis, 5 cases of Guillain-Barré's disease, one case of pseudohypertrophic progressive muscular dystrophy, one case of paralysis of unknown etiology, and 4 "normals." These "normals" included one stenosis of the larynx, two fractures of the femur, and one case which was being observed for possible minimal chorea. These "normals" were run primarily as a check on the method, but also to determine whether the normal curves presented in the literature were applicable to children. It was found in all cases that the amounts of the various electrophoretic components corresponded very closely to the normal values found in the literature. The beta disturbance was present in each case as a very narrow and sharp peak.

Table I shows a tabulation of the cases studied.

Calculations of the proportions of the various electrophoretic components present did not reveal any consistent differences between normal and pathologic sera.

However, as shown in Table I, there were some striking changes in the beta disturbance. In the table these changes are classified as 0 to 3+, where 0 is taken to mean no change in the normal beta disturbance and 3+ is taken to mean the complete disappearance of the beta disturbance. 1+ is taken to mean a definite diminution of the beta disturbance and 2+ to mean a very marked decrease of the beta disturbance but not its complete disappearance. Fig. 1 illustrates characteristic patterns for each type.

From Table I it will be noted that there are 26 electrophoretic determinations here reported on the sera of 23 cases of poliomyelitis. Three of these determinations, Nos. 25, 30, and 40, are follow-up determinations on the sera of patients Nos. 4, 5, and 36, respectively. The results of these three pairs of determinations are especially noteworthy and will be discussed briefly.

In the first of these cases blood was drawn from the patient (M. T.) on the tenth day after the onset of symptoms of acute anterior poliomyelitis and again on the one hundred and seventh day after the onset. The first of these determinations (No. 4) showed a 2+ change in the beta disturbance, whereas the second (No. 25) showed only a 1+ change in the beta disturbance.

In the second of these cases (D. L.) blood was drawn on the fourteenth day (No. 5) and again on the two hundred thirty-eighth day (No. 30) after the onset of symptoms of acute anterior poliomyelitis. The first of these determinations (No. 5) showed a 2+ change in the beta disturbance, whereas the second (No. 30) showed only a 1+ change. The electrophoretic diagrams of this case are shown in Fig. 1, where B and C show, respectively, determination No. 30 (two hundred thirty-eighth day) and determination No. 5 (fourteenth day).

In the third of these cases (G. P.) blood was drawn on the eighth day (No. 36) and on the nineteenth day (No. 40) after the onset of symptoms of acute anterior poliomyelitis. The first of these determinations showed no essential change from the normal beta disturbance. The second of these determinations, eleven days later, showed a definite (1+) change in the beta disturbance. These two electrophoretic diagrams are shown in Fig. 2.

It may be seen from these three cases that changes in the beta disturbance became less conspicuous after a considerable period of time than they had been

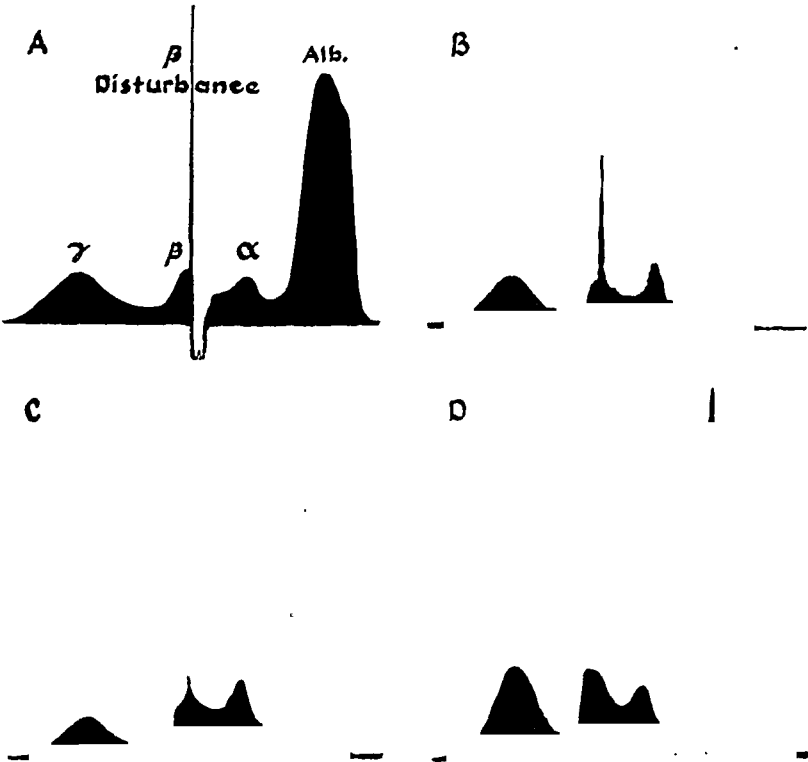


Fig. 1.—Typical electrophoretic patterns illustrating the changes that occur in polio-myelitis. A, normal (No. 1); B, 1+ change in beta disturbance (No. 30); C, 2+ change in beta disturbance (No. 5); D, 3+ change in beta disturbance (No. 15).

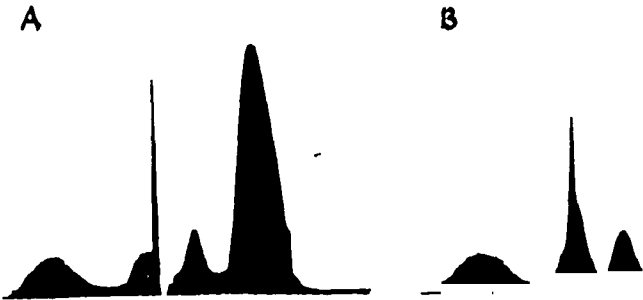


Fig. 2.—Change in electrophoretic pattern of blood serum of polio-myelitis patient (G. P.) with time after onset of symptoms. A, 8 days after onset; B, 19 days after onset.

earlier in the course of the disease (M. T. and D. L.) and that relatively early in the course of the disease the change in the beta disturbance increased with time (G. P.).

From Table I it will be noted that in all determinations of electrophoretic patterns of the sera of patients known to have had poliomyelitis, with the exceptions of determinations Nos. 36 and 18, there were definite deviations from the normal noted in the beta disturbance. Determination No. 36, as mentioned before, was on the eighth day after the onset of symptoms and was apparently too early in the course of the disease, in this particular case, to detect changes in the beta disturbance, since on the nineteenth day there were definite changes detected. Determination No. 18, on the other hand, was on the two hundred sixtieth day after the onset of the illness. Although in certain other cases the changes in the beta disturbance persisted over longer periods of time than this, it seems possible that changes in the beta disturbance had occurred earlier in the course of the illness but had disappeared by this time.

It will also be noted from Table I that there were apparent deviations from the normal in the beta disturbance as early as six days and as late as twenty-two years after the onset of symptoms of poliomyelitis. There was no correlation between the degree of change and the time since onset of illness. Also there was no apparent correlation between the degree of change in the beta disturbance and the severity of symptoms.

Two other variations from the normal electrophoretic pattern were apparent in the electrophoretic patterns of the sera of patients with poliomyelitis in some instances, but not consistently enough to be considered significant. These were: (1) a splitting of the albumin peak and (2) an elevation of the alpha-globulin-beta-globulin interphase (that part of the curve between the alpha-globulin peak and the beta-globulin peak). The first of these variations is well illustrated by Fig. 1, B and the second by Fig. 1, C.

The five cases of Guillain-Barré's disease (encephalomyeloradiculitis) studied gave results entirely similar to those of the poliomyelitis cases. The electrophoretic patterns obtained in these cases were in no way distinguishable from those obtained in the cases of poliomyelitis.

On the other hand, the case of pseudohypertrophic progressive muscular dystrophy and the case of paralysis of unknown etiology included in this report yielded electrophoretic patterns which corresponded well with the normal serum pattern and had none of the characteristics shown by the patterns of sera from cases of poliomyelitis and of Guillain-Barré's disease.

While the incidence of a marked degree of abnormality of the beta disturbance in the patterns obtained on poliomyelitis and encephalomyeloradiculitis sera is a very positive finding, the interpretation of this fact and its significance with regard to these diseases must remain in doubt. There is evidence<sup>14</sup> that the disturbance is associated with a weak lipoprotein complex existing in the components of the beta globulins which becomes partially dissociated when the beta components are under the influence of an electric field in the absence of the albumin and alpha globulin components of the serum (i.e., in the descending



and counterforce to permit anything but continued individual care. This being so, they will also continue to require individual control of their growth and development.

Accordingly, the need for checking infant growth is not lessened simply because infant feeding has been successful, or because good results have been observed without benefit of precise methods for evaluating growth. In fact, the practical need for close control is even more urgent than in former times. Once the example has been set, the responsibility for attaining top quality is obviously increased, and it therefore becomes still more important to know how well a given baby is fulfilling his own capacity for growth.

#### DIFFICULTIES IN THE USUAL TYPES OF APPRAISAL

A baby's health, physical condition, and progress are so related that his feeding and care are governed to a large extent by what can be determined about his growth and development. For this purpose, information is sought, as a rule, from three sources: (1) history and physical examination of the baby, (2) *clinical experience, as a background for evaluating the findings*, and (3) body measurements such as weight and length, among others. In arraying the evidence from these different sources, certain difficulties are always encountered, and a brief explanation of them will indicate what the Baby Grid has been designed to overcome.

If judgment is based solely on (1) and (2), it is formed entirely of subjective impressions that are more appropriate to the evaluation of the baby itself, as reflected by the medical findings of his physical condition, than to conclusions on his growth, which, in this case, are exceedingly indirect. Therefore, to obtain data on growth as a distinct element, weighing and measuring babies has become permanently established as a pediatric procedure.

Nevertheless, even though weight and length have the advantage over physical findings of being objective representatives of body changes associated with growth and development, they convey much less information than is expected of them. In other words, the basic measurements of weight and length which are taken for the purpose of making clinical judgment more certain, do not carry their own significance with them. What that is must be elicited by some method of treating the data.

However, the usual methods of dealing with a baby's measurements have yielded so little information as to throw doubt on the practical value of the data, and, unfortunately, to discourage the practice of weighing and measuring babies. When this is done, it eliminates the only objective support that clinical judgment can command.

While full details concerning this unsatisfactory situation have been given elsewhere,<sup>2, 3</sup> the main causes can be stated briefly. For instance, the only asset a simple weight curve possesses is its internal consistency, and yet even regularity may be misleading. Furthermore, to compare a baby's weight with the usual standards is technically incorrect, as ought to be evident from the very individualism that babies display. This, in fact, excludes the right to apply age averages of whatever kind, whether means, medians, or percentiles,

in tabular or curve form, because these fail, among other things, to make due allowance for individual differences in physique, an item that cannot be disregarded in attempting to appraise either a baby or his growth.<sup>2</sup> Although such standards are in common use today, the time and effort involved are hardly repaid, since the results are given no serious consideration.

Moreover, comparing two separate age curves of weight and length in order to obtain an idea about body build is confusing, particularly if the data are charted in deviation form. These methods leave the identification of so concrete an attribute too much to the imagination, especially since it is possible, as the Baby Grid shows, to determine physique very precisely and to display the results without ambiguity. Finally, empirical rules, such as doubling the birth weight in from five to six months and tripling it in a year, fall far short of providing adequate guidance.

Thus the traditional methods of dealing with weight and length, which involve matching the values of a given baby with tables, curves, or rules of one kind or another, have failed to be useful because they do not at the same time include a suitable basis for interpreting the measurements of individual babies. To be specific, they do not supply standards for judging the quality of individual growth performance.

#### OBJECTIVES

In view of the foregoing, the broad practical purpose of the Baby Grid is to bring out the significance of an infant's measurements so as to make the interpretation of the results not only objective but also as accurate and as obvious as possible. Its particular aim is to deal with the ever-recurring question of whether growth and development in a given infant is or is not satisfactory. Put otherwise, this is simply a matter of determining the quality of growth. Consequently, the purpose of the Baby Grid is to furnish the yardsticks, the standards of individual performance, and, in brief, a self-contained method for measuring, recording, and displaying the quality of growth directly. It seeks to make a baby's growth and development more nearly the guide to infant feeding and care that they are supposed to be.

#### RANGE OF OPERATION

As previously shown,<sup>3, 6</sup> the principles of the Grid technique operate throughout the long span of human development marked at its lower end by an embryo weighing 1 Gm. and at the other by the most extreme examples of gigantism and obesity. Within this interval the Baby Grid provides a control chart on the quality of infant growth and development between birth and 3 years. As such, it applies not only to the case of full-term infants but also to premature babies weighing as little as 1,000 Gm. or having a body length of only 12 to 13 inches.

Consequently, by establishing these standards of performance in its own field, and by uniting them into a single formulation of law and procedure that holds both for premature as well as for full-term infants, the Baby Grid bridges a gap that has remained open until now.

## EVALUATION OF GROWTH QUALITY IN INFANTS

*Preliminary Approach.*—Even without previous description, the curves of Figs. 1 to 7 illustrate how simply the quality of an infant's growth may be ascertained and recorded by plotting his weight and length on a Baby Grid from time to time. The results, in fact, are practically self-evident, since the significance of the original measurements is directly revealed in terms of the fidelity with which the curves of these different infants conform to certain obvious patterns of the Grid. Where the basic trends are followed, one infers without second thought that growth quality is, and has been well controlled; the steadier the curves, the more certain this conclusion. Where trends break, even the first stages of deviation are readily recognized, and they are sufficient to place the quality of growth in question; the greater the departures, the more certain it is that growth is not under control and therefore faulty.

*Structure of the Baby Grid.*—Panels A, B, C in Fig. 1 contain the channel system, 1 to 5, the standard schedules of development (auxodromes) numbered 7, 8, and 9, and energy scales, respectively. All these operate just as they do in the Big Grid for older children.

*Panel A. The Channel System:* As before, the plan of the channel system provides a field or map in which the position of points plotted from the original measurements of a baby's weight and length (scales *a*, *b*) may readily be identified by channel and by cross-graduated levels (6).

In the Baby Grid, however, there are two parts to the channel system: the left half, 3, 4, 5, represented by channels  $A_{12}$ - $A_5$  is required because babies do not normally travel along the main line of human development represented by the right half, 1, 2, the original  $A_3$ - $M$ - $B_3$  group of this compound system. They travel these side tracks of infancy because they are naturally more chubby than the older children on the main line or than they themselves were during intrauterine life.<sup>6</sup> The direction of the course they take through the channel system is indicated by the central (yellow) shaded path, 3, 4, 5. Thriving premature babies traverse the lower portion, 3, which joins the full-term strip where the weight-length points of normal newborn infants are found, 4. Thenceforward the path is strictly up-channel until it begins to bear right on its way toward re-entry on the main line. The turn, 5, is reached in about eleven to twelve months by average babies.

The purpose of the channel system is again threefold: (a) to act as a kind of direction finder for ascertaining the *trend* of a baby's own curve as

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Fig. 1.—The Baby Grid (front). Panels A, B contain the channel system or grid proper, 1, 2, 3, 4, 5, the standard schedules of development, 7, 8, 9, for advanced, average, and premature babies, respectively. Panel C contains the scales for energy requirements and energy quotients: *a*, weight scale in kilograms and pounds, *b*, length scale in centimeters and inches; *c-d* the channel curve of a baby girl twin, *e-f* the corresponding auxodrome obtained by plotting the levels of respective points in the channel system, Column 5 against age, Column 2. Note ample space allowance for the newborn period, *e*. D, E, subsidiary panels for charting chest and head circumferences, Columns, 6, 7. Thriving premature babies follow the shaded path, 3; the weight-length points of "average" full-term infants are found in the region, 4; 5, the upper turn of the infant path usually reached at 11-12 months; 6, level lines of development which measure the size of a baby in terms of body surface, see table of Useful Data lower left, and reproduction, Table II. The *d* values of these level lines indicate that the baby is approaching more and more the standard 8, is consistently satisfactory. *c-d* and *e-f* in comparison with the trends of the path 4-5-*d* and of the standard 8, is consistently satisfactory.



## Grid

Progress during Infancy

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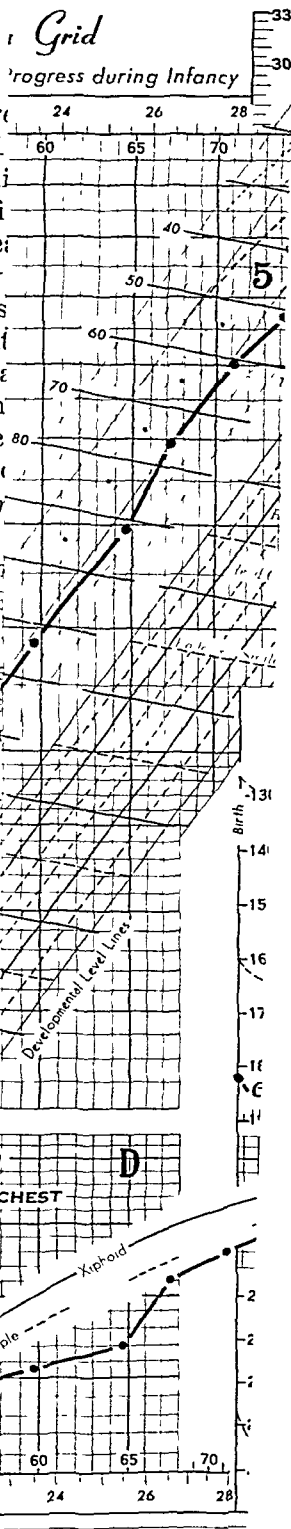
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plotted from the data on weight and length; (b) to measure a baby's size by means of the level at which various weight-length points are located, for each level represents a different value of body surface<sup>6\*</sup> and (c) to identify a baby's physique or shape by the channel the points fall into, chubbiness increasing in channels toward the left and slenderness toward the right in accordance with the scheme of Table I.

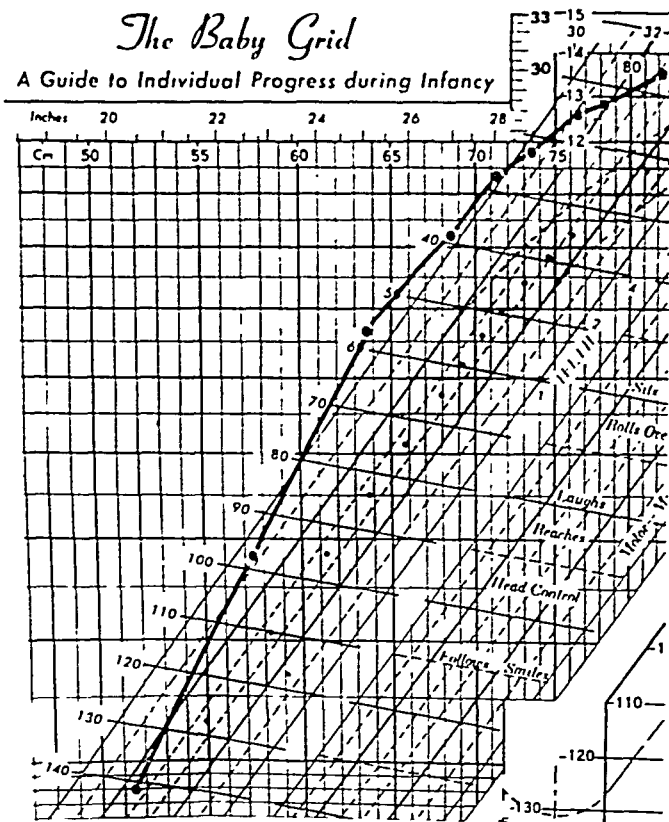


Fig. 2.—Typical response to overeating. A good robust baby in 4½ at Level 141, getting fatter as his curve proceeds outward. Extremely fat at Level 60. Note, however, that he rounded the curve in normal fashion at levels that would be expected from his earlier course. Mother "poured food into him."

Although a baby's size (surface) obviously increases as he proceeds along the channel system (Table II) the numerical value of the level lines diminishes. This indicates simply that, as a baby advances, he is coming closer and closer to the end of infancy at about level 0.

As a guide to the closely associated events of motor-mental development, the appearance of *smiling*, *head control*, *rolling over*, *sitting*, *standing*, etc., is indicated by labels in the right hand channel system at the levels of physical development where these events may normally be expected to occur. Their inclusion in this schedule form should help to focus attention upon, and to emphasize the connections between physical, mental, and motor development.

\*See introductory footnote.





Fig. 3.

Fig. 3.—Clear-cut channel shifts: A, at the time this boy's father went to war; B, measles. Note subsequent complete recovery to central path, as expected.

Fig. 4.—The path of an initially small, but later, of a thriving premature baby. Physiologic loss followed by excellent reorientation of direction.

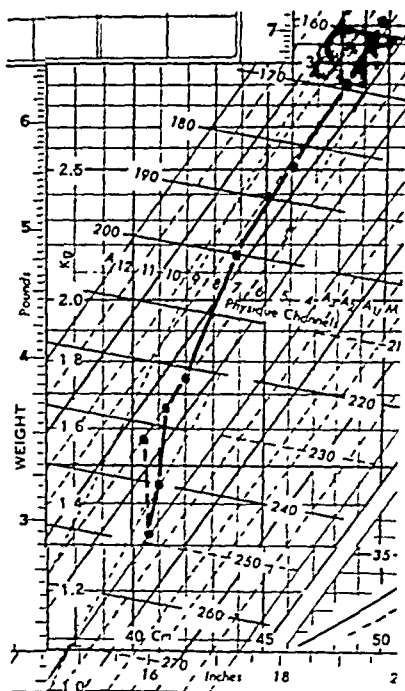


Fig. 4.

TABLE II  
USEFUL DATA

Le el	Body Surface	Food Vol			DIET—Grams			Human Milk	Human Milk x 10	Riboflavin
		cc	cc	cc	Carb	F.P	C-F-P			
250	094	75	45	15	4-7	..	..	63	12	
220	105	50	54	20	5-8	..	..	10	15	
210	123	105	65	23	6-9	..	..	..	..	
200	140	130	78	26	7-10	..	..	..	..	
190	160	156	94	30	7-12	..	..	13	20	
180	171	170	102	32	8-12	..	..	16	24	
170	183	187	112	35	11	..	..	19	28	
160	196	205	123	39	12	35-16-6	..	21	32	
150	209	225	135	43	13	35-18-6	..	25	33	
140	224	247	148	47	14	42-19-7	..	31	45	
130	239	270	162	52	15	45-21-8	..	34	51	
120	256	285	178	57	17	51-23-8	..	41	62	
110	273	325	195	63	19	55-25-9	..	43	72	
100	292	355	215	69	21	62-29-10	..	52	78	
90	312	392	235	75	23	67-31-11	..	60	90	
80	334	431	255	83	25	74-34-12	..	75	113	
70	357	470	275	92	28	81-33-14	..	..	..	
60	381	515	310	107	31	..	..	..	..	
50	405	565	340	107	33	..	..	..	..	
40	426	595	372	117	35	..	..	..	..	
30	445	625	410	125	38	..	..	..	..	
20	465	655	445	135	42	..	..	..	..	
10	532	840	495	145	45	..	..	..	..	
0	569	915	540	155	48	..	..	..	..	
-10	605	1000	595	165	52	..	..	..	..	
-20	650	1100	650	180	55	..	..	..	..	
Vitamin A 1000-2900 IU Vitamin D 400-800 IU Ascorbic Acid 20-40 mg Ca 0.5-1.0, P 11-14 g										
					Fe	6.00-7.00 mg				
					Cu	0.60-0.70 mg				
					Mn	0.75-3.75 mg				
					I	0.01-0.04 mg				



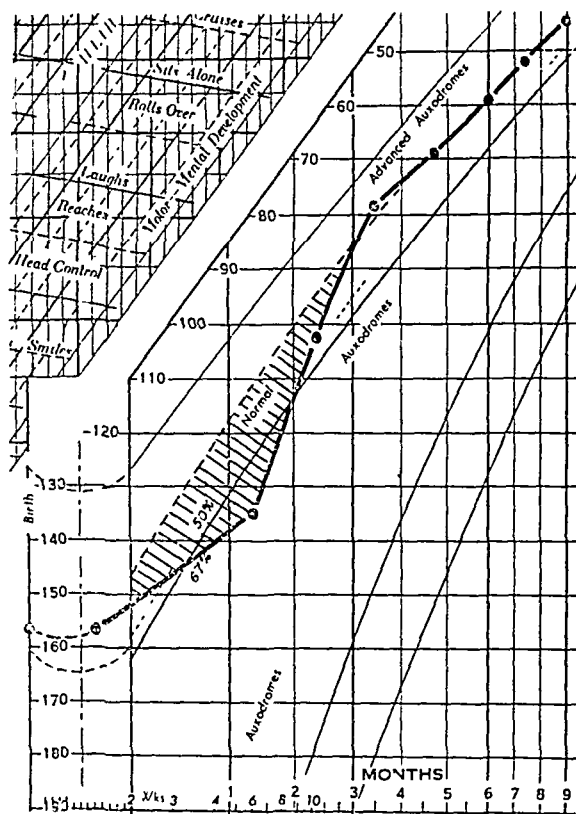


Fig. 5.—Slow start in a baby with feeding difficulty. Recovery after the sixth week and thereupon steady progress along auxodrome expected on basis of birth weight.

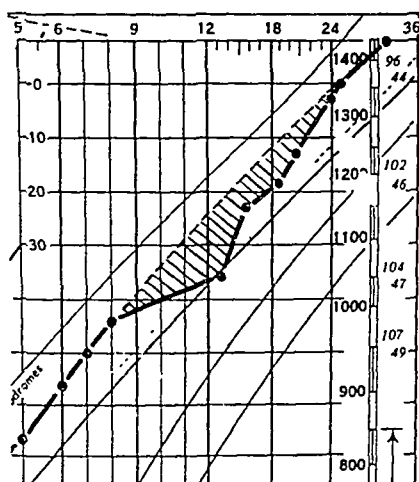


Fig. 6.—Excellent adherence to own auxodrome up to the eighth month when family was forced to undergo repeated changes of residence. Dashed projection shows expected auxodrome. Cross-hatched area proportional to fuel debt.\* Vertical distances between expected and actual auxodrome measure lag, that is, the number of levels the baby is in arrears at a given age. Full recovery when home had been resettled.

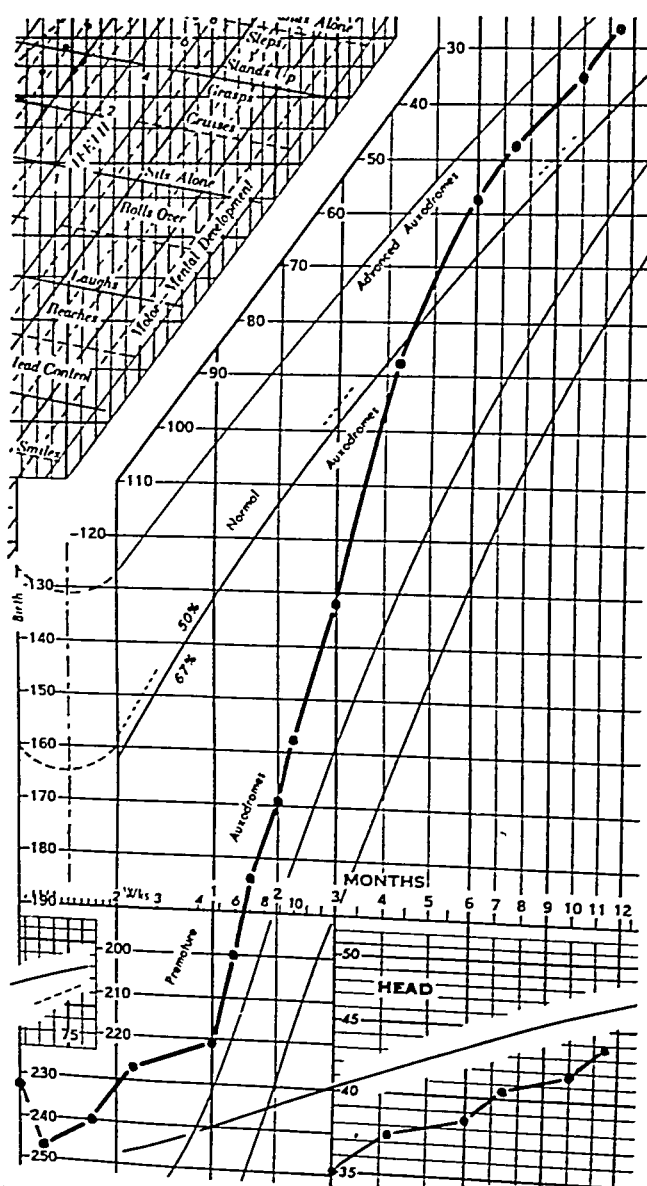


Fig. 7.—The auxodrome of the premature baby in Fig. 4. After the first month's difficulties in getting started, this baby made up time (and distance) to proceed at normal speeds along a comparatively advanced auxodrome after the age of 6 months.

## DIRECTIONS

To make out a Baby Grid record proceed as follows: (Compare Fig. 1.)

*Step 1.* Record name and birth date above ruled table at upper left. Enter date of observation, age, weight, length, head and chest circumferences.

*Step 2.* Plot weight against body length in Panel A. Use vertical (*a*) scale for either kilograms or pounds and ounces, and horizontal (*b*) scale for centimeters or inches.

*Step 3.* Read *developmental* level from black diagonal scale along green channel system and insert the value in Column 5 of ruled table.

*Step 4.* Plot level as just read against corresponding age in Panel B to locate position of baby's auxodrome.

Repeat steps one to four for each observation and draw the curves point to point. Complete record by plotting chest circumference against body length in Panel D and head circumference against age in Panel C.

To use Motor-Mental Development Scale note that a baby may normally be expected to follow objects when he has reached level 108; to roll over at level 65; to take steps with help at level 32, etc.

To use Calorie-Intake Scale read value corresponding to a given level.

*Suggestions:* For results such as are illustrated in Figs. 1 to 7 which are shown full size, use medium pen and black ink. Check all apparent deviations. When a baby's auxodrome deviates as in Figs. 5 and 6, sketch in the expected auxodrome with a dash line and cross-hatch the lag area in red crayon or ink for maximum contrast.

## PRINCIPLES OF INTERPRETATION

*Direction and Speed of Development.*—The key to the problem of evaluating growth as well as to the mechanism of the Baby Grid is found in the pertinent but often neglected fact that growth is a *moving* and not a *static* function in babies, or for that matter in any organism.<sup>3</sup> It is for this reason that a mother asks, intuitively, how her baby "is doing," rather than how he "is." This fact also explains why it is more significant to know, not what a baby weighs or how long he is, but instead, what that baby is accomplishing with the weight and length he does have.

A baby's growth, then, is best characterized in terms of its *direction* and *speed*. This, however, implies two things: (1) methods for measuring direction and speed, and (2) tolerance limits by which it is possible to determine whether direction and speed in a given infant, and throughout a given interval, conform to standards of performance shown by actual experience to be acceptable. Both (1) and (2) are furnished as a single procedure in the Baby Grid.

The direction of a baby's development is revealed with the help of the channel system, and the acceptability of a given direction is defined in terms of individual channel width. Thus, for example, many infants will follow the direction of the channel system over the straightaway portion of their course so precisely that point after point will fall not merely within the narrow limits of the same channel, no matter which this happens to be, but almost exactly

on the very same line. That is top quality direction. Ordinarily, shifts of one channel in twenty levels of forward advancement are acceptable, but even these should not persist. Normally, they will be compensated after an equal forward advance. On the turns, a baby's curve should follow the trend of the shaded pink and yellow path with corresponding certainty.

Similarly, in the case of speed, a baby's auxodrome ought not fail, without good explanation, to keep within two to three levels of running parallel with a near-by standard.

*Quality Control of Growth in Individual Infants.*—The question as to whether a particular infant is, or is not doing well is therefore very directly answered so far as objective information is concerned by noting (a) how closely that baby's curve in the channel system is following the direction of *all* healthy babies at the same stage or level of development, and (b) how nearly the baby is keeping up with one of the standard schedules; that is, whether it is progressing from level to level as rapidly as is called for by that schedule of development.

Direct quality control on growth may therefore be considered as established when an infant's measurements have actually been made to demonstrate that the direction and speed of his development are both being maintained within the foregoing tolerance limits of allowable variation. Fluctuation within these limits is due solely to chance. By contrast, deviations outside these limits indicate, apart from frank errors, that the departures should be considered the result of trouble, and hence that the babies who fail this test of quality should be examined for cause. (See Figs. 2, 3, 5, 6 and 8.)

## RESULTS

The curves in Figs. 1 to 7 illustrate typical problems that are encountered in practice.\*

\*The examples and results illustrated here in Figs. 1 to 7 have been selected from a series of about 1,800 Baby Grid records under current study. No attempt is made to classify this series further, since the results could reflect merely local conditions at the moment and since they could not possibly have any bearing on the accuracy or the validity of the Baby Grid. This point should be emphasized because the question is sometimes raised as to how many "cases" have been employed "to test" the Grid technique. Consideration of the methods used to develop this technique will help to explain the limitations of any admissible tests. The operation of the Baby Grid involves two fundamental principles and two only, namely, the direction and speed of human development; other principles, such as are involved in the question of physique, size, and energy relations, are subsidiary.

As regards direction the data of the past 100 years covering the range of human development from embryonic life to stages of gigantism are sufficient to determine this direction to within 43 seconds of arc.<sup>6</sup> Moreover, it can be shown that any significant deviation from this will ultimately lead to abnormal body contours. The principle of shape, and the designation of shape by channels is merely a consequence of this extremely precise orientation of growth. One does not, therefore, attempt to channelize babies or children, they actually do this themselves by maintaining the fundamental direction of development, which, incidentally, differs by only 1 degree 3 minutes of arc from the direction typical geometrical bodies would take, if they, too, developed to greater sizes.<sup>6</sup>

As regards speed, it may be remarked that early (1875-1900) data on breast-fed infants conform well to present auxodrome standards, but that the contemporary observations on artificially fed babies do not meet these standards satisfactorily. As presently conducted, artificial feeding does support the same speed of development characteristic of healthy breast-fed babies.

Consequently, the demonstration that a baby does or does not follow these basic norms of direction and speed is not so much a test of the Grid as it is of the baby. Since it would be possible to select any number of babies who do follow the Grid standards, as well as any number who do not, at least over certain intervals such selections remain arbitrary and cannot decide for or against those elements that are intrinsically a property of human development.

It may, nevertheless, be added that recent data from large-scale studies so ably and faithfully assembled by Krogman<sup>7</sup> all bear out the Grid specifications of direction and speed, a result that is plainly apparent in the original data of Quetelet reported more than a century ago, and in all major observations since then.<sup>8</sup>

*Direction.*—The steady forward course of the baby girl twin in Fig. 1 shows how closely a healthy, thriving infant will maintain a channelwise direction of development along the straightaway, and hence a constant physique over that portion of the path. Her curve along the lower border of the yellow path, that is, along  $A_7$ , represents a degree of chubbiness that remains consistently just less than average but hardly enough less to call slender or thin.

By contrast, the curve in Fig. 2 shows a boy getting overly fat because his mother kept "pouring food into him" in the belief that he, like the rest of the family, was living to eat. The opposite effect is shown by the curve in Fig. 3. This boy started out well as an average baby. He fell victim to his father's going to war at  $A$ , and to measles at  $B$ , but finally recovered his expected central channel position.

The small premature baby in Fig. 4, after his initial loss to level 249 in  $A_4$ , where he looked "scrawny," steered an excellent uneventful course through the shaded path, thereby becoming five and one-half channels more robust and chubby at level 158 in  $A_8$  than he had originally been.

*Speed.*—The auxodrome of the twin in Fig. 1 conforms to the neighboring standards, 8 and 9, on either side of it. At point after point this baby reached expected levels on time. Following a good start, speed of development was up to par.

The curve of Fig. 5 is that of a baby with feeding difficulty whose start was slow but whose development picked up sufficient speed to enable him to proceed along his own schedule after the tenth week.

In Fig. 6, excellent progress up to the eighth month is interrupted by several cross-country changes of residence, a few minor infections, and a generally unsettled home. Speed is lost during the slow-down but is accelerated during recovery. At normal speed the baby would have continued to progress along the upper broken projection. The cross-hatched area between this as the upper and the actual auxodrome as the lower border is proportional to the fuel debt<sup>3</sup> which must be made up preliminary to full recovery. Vertical differences between expected and actual auxodromes measure the amount of lag in levels at any given age, as 36-21, or fifteen levels of lag at  $13\frac{1}{2}$  months, but only about five at 21 months.

The auxodrome of Fig. 7 is that of the small premature baby whose channel course is shown in Fig. 4. After the first month's difficulties had been overcome the infant made up for lost time, ultimately finding his own proper schedule by the age of 6 months. While most premature babies will follow along in the region between standards 8 and 9 (Fig. 1) a few, such as the baby of Fig. 7, will manifest a tendency to reach and thereafter to pursue more advanced schedules without in any sense being pushed to do so. Such infants, it may reasonably be assumed, would have been equally advanced had they gone on to term.

#### REMARKS

The foregoing examples in Figs. 1 to 7 taken together show how simple it is, by means of the Baby Grid, to apply the principles of direction and speed

to the problem of evaluating the quality of growth in individual infants, despite great differences in their types, size, and age. Besides illustrating how notably uniform growth and development normally are, these examples also demonstrate how soon a given departure can indicate that growth is unacceptable, or at least in question. In all of these cases, they illustrate the manner in which a baby's growth can routinely support clinical estimates of his condition and thus serve as an objective guide to the management of his feeding and care.

#### SUMMARY

The Baby Grid is a direct-reading, control chart on infant growth including that of premature babies weighing as little as 1,000 Gm. It has been designed to pictorialize the growth and development of a given infant during its first three years, and to do this so as to make the quality of growth self-evident at a single glance.

Babies are too individualistic and their growth too much at the mercy of force and counterforce to permit anything but individual care, and accordingly, individual control of their development. Attainment of top quality presumes knowledge on how well a given baby is fulfilling his own capacity for growth. The answer to this ever-recurring question of pediatrics is directly revealed in terms of the fidelity with which a baby's measurements of weight and length conform to the Grid standards of direction and speed of physical development. These are the decisive elements to be evaluated because of the pertinent but often neglected fact that growth is a moving, not a static function in babies. The Baby Grid thus seeks to make an infant's growth more nearly the objective guide to the management of his feeding and care that it is supposed to be.

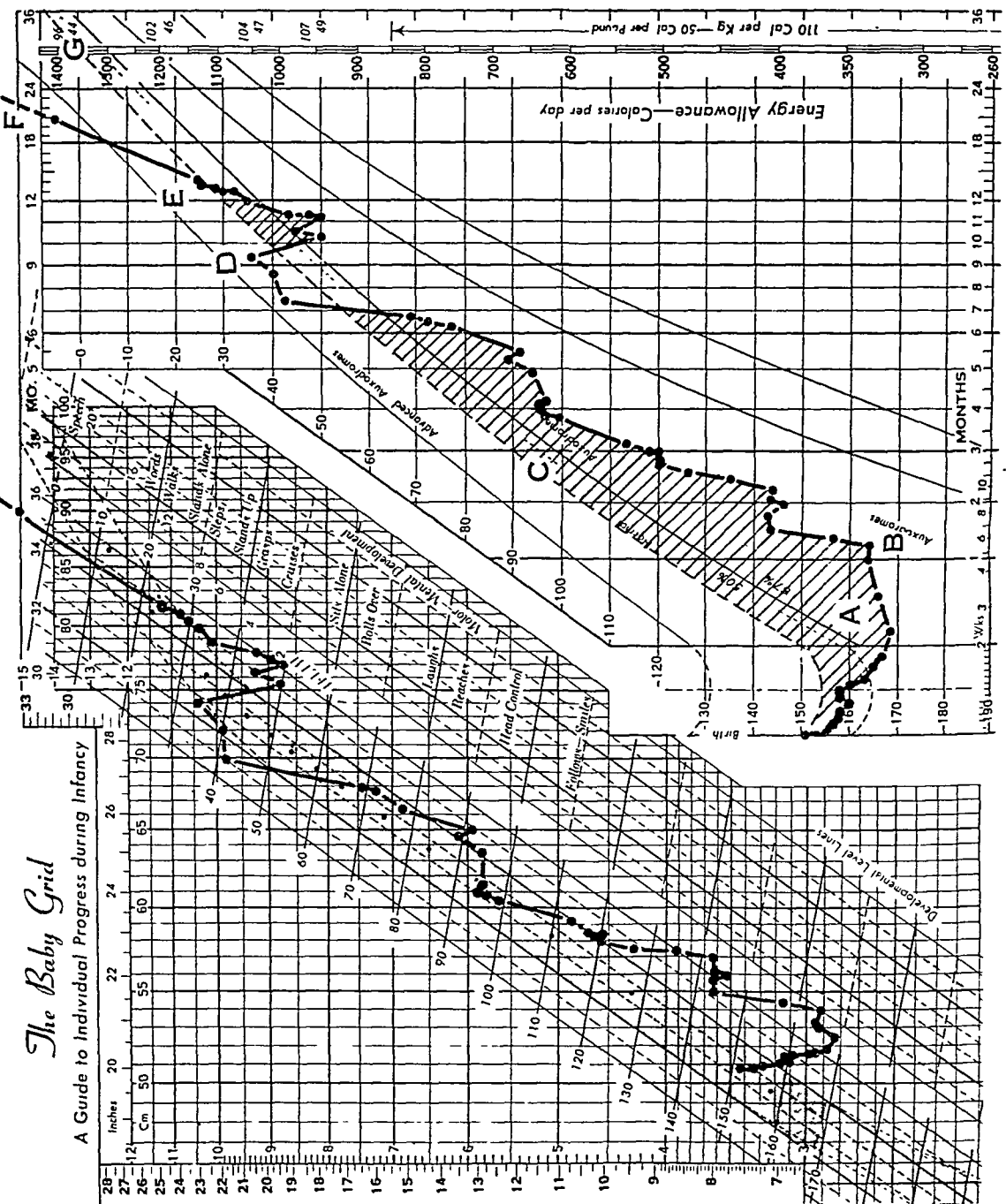
#### ADDENDUM

A striking example of how the Baby Grid pictorializes the bizarre effects on infant growth and development that must be expected from the profound disturbance caused by the dual lesion—congenital adrenal cortical insufficiency associated with macrogenitosomia due to hypersecretion of androgenic hormone—is obtained from the data in Thelander's recent report,\* which summarizes the history of a boy followed from birth, whose course up to 14 months had been described earlier,† and who died at 6 years of age in an attack of measles. These papers furnish a unique set of observations along with measurements on body weight and length, the resulting Baby Grid record for the first two years being shown in Fig. 8.

Since only three values for body length up to 14 months were reported, in comparison with many measurements of weight, linear interpolation was employed to estimate length at ages for which weights, but not lengths, were given. This procedure was clearly justified by the consistency of the original length measurements which were distributed at almost equal intervals between birth and 14 months and which formed a smooth, not an erratic, curve. Full

\*J. PEDIAT. 29: 213, 1946.

†J. PEDIAT. 18: 779, 1941.



use could thus be made of the weight data so that Fig. 8 represents the best Grid estimate that can be constructed out of the known facts.

Viewed as a whole, the curves in Fig. 8 clearly reflect not only the fundamental trends and tendencies of growth and development in this unusual affliction but also the effects of treatment as well. Particularly noteworthy and instructive are: (1) instability, attributable, no doubt, to the defective water-salt-hormone metabolism; (2) prolonged neonatal failure to initiate growth until Percorten was administered; (3) dependence of growth on continued administration of the hormone in some form; (4) severe reaction to an otherwise mild attack of exanthem subitum; and (5) a two- to threefold increase in the rate of physical development. The latter enabled the infant to regain a 42 level lag handicap at 1 month by the time he had reached the age of  $7\frac{1}{2}$  months. Following his roseola (9-13 months) it also had the effect of propelling him at almost triple speed far beyond his "expected" levels, 8 and +7, respectively, at 2 and 3 years, as represented by the dashed auxodrome.

His later course graphed on a Big Grid and discussed more fully in forthcoming articles\* shows that this uninhibited burst of speed persisted after the lag-gap had once been closed at 14 months so that he reached level 115 by the age of 6 years, that is, a level attained by a boy on the 67 per cent auxodrome at 12.75 years. From 1 to  $7\frac{1}{2}$  months, high speed was mainly a "recovery" phenomenon; but the continued surge of the auxodrome between 14 and 24 months, as well as thereafter, must be ascribed to overproduction of androgenic hormone, since the effects it represents compare with the results that are found in early gigantism. Contrary to Thelander's opinion, based on the height-age curve, that this boy's "ultimate height . . . would have been below average," Grid analysis of these data would, if anything, suggest ultimate gigantism, provided, of course, that the epiphyses remained open. For the auxodrome of Thelander's patient is, in fact, headed almost directly toward the same point reached by a notable pituitary giant, namely,  $A_1$ -189 at 9 years!<sup>16</sup> So far as the growth data go there is nothing up to the last observation at 6 years to suggest that the auxodrome was within a year or so of reaching its upper limit in spite of advanced bone age findings. Accordingly, there is no Grid basis for expecting premature closure as a result of impending gonadotropic action. It seems altogether more likely that this boy was destined for excessive rather than for curtailed stature.

Apart from these implications, the curves of Fig. 8 as compared with the steady trends in Fig. 1 afford an excellent illustration of great differences in

\*In preparation for *Brenneman's Practice of Pediatrics*, Irvine McQuarrie, Editor, W. F. Pryor Company, Inc., Hagerstown Md.; and for *Therapeutics of Infancy and Childhood*, Harry R. Litchfield and Leon Dembo, Editors, F. A. Davis Company, Philadelphia.

Fig. 8.—Unstable growth and development in congenital adrenal cortical insufficiency associated with macrogenitosomia as reconstructed from the recent data by Thelander discussed in the addendum to this paper. Note prolonged failure to regain birth level, A, until Percorten was administered, B, at about the sixth week thereafter a definite but somewhat irregular recovery to more central channel pathways (improved physique) as well as to expected auxodrome, C, lag-gap being closed at  $7\frac{1}{2}$  months. Reaction, D-E, due to exanthem subitum. Path, E-F, shows persisting elevation of speed resulting in attainment of levels far in advance of expected segment, E-G. Segment, B-E, a "recovery" phenomenon; segment, all probability due to oversecretion of androgenic hormone.



"growth quality" within the limits of attainable control and of how simply these effects may be portrayed.

The author is particularly indebted to Miss Mary E. Sweeny and to Miss Marian E. Breckenridge of the Merrill-Palmer School, Detroit, for placing many of their long-term careful records at his disposal. The final stages of design and construction of the Baby Grid were greatly expedited by this opportunity to study their data objectively and then to compare the results with their personal observations and histories of those infants and children.

The author is also greatly indebted to Drs. Spencer A. Wahl, Joseph E. McClelland, John D. Nourse, and Robert B. Hauver for their kindness in providing case observations made under the conditions of actual practice.

#### REFERENCES

1. Wetzel, N. C.: J. A. M. A. 116: 1187, 1941.
2. Wetzel, N. C.: J. PEDIAT. 22: 82, 208, 329, 1943.
3. Wetzel, N. C.: Growth, Medical Physics, Chicago, 1944, Year Book Publishers.
4. (a) Breckenridge, Marian E., and Vincent, E. Lee: Child Development, Philadelphia, 1943, W. B. Saunders Co., p. 236.
- (b) Brody, Samuel: Bioenergetics and Growth, New York, 1945, Reinhold Pub. Corp., p. 638.
- (c) Scramlin, E. Nancy: Hoosier Health Herald 27: 83, 1946.
- (d) Benz, Gladys: Pediatric Nursing, St. Louis, The C. V. Mosby Company. To be published.
5. Child Growth and Development Emphases in Teacher Education, Prepared by the 1943-1944 Teachers College Collaborators, Lonzo Jones, Chairman, American Association of Teachers Colleges, p. 23. (Systematic use of the Grid in School Medical Health Service such as recommended in this report is being carried out in various communities, notably: In Oneonta, New York, under the direction of Dr. Francis H. Marx, Director of School Physicians; in the Delta County Schools, Escanaba, Michigan, under supervision of C. P. Titus, Commissioner; in Crawford County, Ill., Bryan Heise, Director of Extension Service; in Detroit, Citizen's Evaluation Study Committee, Arnold K. Meier, Director; in Corpus Christi, Texas, Independent School District, M. P. Baker, Superintendent.) Similar large-scale use of the Grid is being made by Captain I. T. Thacker in Boy's Brigades, Physical Training Battalion, Kimberley, South Africa; in the School Districts of Clayton, Mo., Everett, Mass., Winston-Salem, N. C., Grant's Pass, Ore., Shaker Heights and East Cleveland, Ohio. For pediatric appraisal the Grid is being employed in various institutions and departments such as: The Laboratory Schools, University of Chicago; St. Louis Children's Hospital; and Henry Ford Hospital, Detroit.
6. Wetzel, N. C.: Mass, Volume, Surface and Energy Relationships in Human Growth and Their Application to the Problem of Growth Failure in Children, Cleveland Engineering 39: 5, 1946.
7. Bruch, Hilda: J. A. M. A. 118: 1289, 1942.
8. Beal, V. A., Burke, B. S., and Stuart, H. C.: Am. J. Dis. Child. 70: 214, 1945.
9. Krogman, W. M.: Growth of Man, Tabulae Biologicae, The Hague, Uitgeverij Dr. W. Junk, 1941.

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# THE EFFECT OF DIABETIC AND PREDIABETIC PREGNANCIES ON THE FETUS AND NEWBORN INFANT

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IT HAS long been recognized that the diabetic state in the mother has often been associated with many unusual phenomena in the fetus and newborn infant. Among the outstanding peculiarities of these infants there has been noted a high mortality rate, a tendency toward an excessive birth weight and occasional anatomic changes in some of the viscera and glands of internal secretion. Until recently it has been thought that these peculiarities of the offspring were in large part related to the maternal hyperglycemia and the manner in which it was regulated. The excessive size of the fetus was attributed directly to the fact that the fetus was maintained during pregnancy on a high carbohydrate intake. The high fetal mortality was explained either by the occurrence of maternal hyperglycemia or hypoglycemia associated with an inadequate regulation of the diabetes; the high neonatal mortality was considered to be the result of the hypoglycemia induced in the newborn infant by the overactivity of its pancreatic islet tissue. The basis for this theory rested on the observation that in some infants born to diabetic mothers an actual hypertrophy of the islet tissue could be observed. Recent studies indicate that these previously held theories are improbable. There is considerable evidence to show that all the phenomena observed in infants born to diabetic mothers are to be found among infants born before the onset of maternal diabetes. It is the purpose of this paper to review not only this newer evidence but also the recent investigations that have been made on the etiology of the high fetal and neonatal mortality in diabetic pregnancies.

## FETAL AND NEONATAL MORTALITY

The frequent occurrence of fetal deaths before the appearance of diabetic symptoms was first noted by Allen.<sup>1</sup> His findings were corroborated in a study by Miller, Hurwitz, and Kuder.<sup>2</sup> Data taken from the latter report are given in Table I to show the effect of the prediabetic state on the fetal and neonatal mortality rate. The mothers of the infants included in Table I all developed diabetes during the childbearing period and gave birth to infants both before and after the onset of diabetes. It is seen that the fetal and neonatal mortality was about as high during the twenty years preceding the onset of maternal diabetes (19.8 per cent) as it was after the syndrome made its appearance (23.6 per cent). It has also been shown by Miller<sup>3</sup> that there was a high fetal and neonatal mortality rate among the offspring of women even though the mothers

From the Department of Pediatrics, Kansas University School of Medicine.  
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did not develop signs and symptoms of diabetes until after they had reached the fifth and sixth decades of life. The data in Table II are taken from this latter report by Miller. The data in Table II indicate that among infants born less than sixteen years before the onset of maternal diabetes to women who have passed the childbearing period there was a high fetal and neonatal mortality rate (15.9 per cent). Recently Herzstein and Dolger<sup>4</sup> have published data which support the findings in Tables I and II, although their conclusions are at variance with their statistics. They concluded from their findings that "the first five-year prediabetic period revealed an increased fetal and neonatal mortality, but the preceding 15 years was not characterized by such a tendency." Their data show, however, a mortality of 7.5 per cent among 212 infants born during the fifteen years prior to the onset of diabetes in the mothers. This rate is statistically significantly higher than the rate of 3.01 per cent in a group of 398 infants born to nondiabetic women to which they were compared. Herzstein and Dolger failed to see the significance of their own data, partly because they chose to compare mortality rates based on personal interviews with the diabetic mothers, held in some instances many years after the deliveries took place, with infant mortality rates of control groups based on hospital deliveries and actual records made at the time the deliveries occurred.

TABLE I. MORTALITY AMONG FETUSES AND NEWBORN INFANTS DELIVERED DURING PREDIABETIC AND DIABETIC PERIODS

	BIRTHS	FETAL AND NEONATAL DEATHS	DIED (%)
Prediabetic period			
1-5 yr. before onset	79	28	35.4
6-10 yr. before onset	79	10	12.6
11-20 yr. before onset	94	12	12.7
Total before onset	252	50	19.8
Diabetic period	93	22	23.6

TABLE II. FETAL AND NEONATAL MORTALITY OF INFANTS DELIVERED BY WOMEN DEVELOPING DIABETES DURING THE FIFTH AND SIXTH DECADES COMPARED WITH THAT OF INFANTS DELIVERED BY NONDIABETIC WOMEN

	BIRTHS	FETAL AND NEONATAL DEATHS	DIED (%)
Prediabetic period			
1-15 yr. before onset	63	10	15.9
16 yr. or more before onset	201	12	6.0
Total before onset	264	22	8.3
Nondiabetic controls	263	5	2.0

It is not easy to determine the exact onset of diabetes in adults and on that account the mortality rates given for the prediabetic infants are open to criticism. However, the fact that the mortality rates were found to be high ten, fifteen, and twenty years before the onset of recognizable signs and symptoms, particularly as is demonstrated in Table I, tends to obviate the criticism that the date of onset of the diabetes cannot be absolutely stated.

## BIRTH WEIGHT

The tendency toward an increased birth weight among infants born to diabetic mothers is recognized by all. A similar tendency prior to the inception of maternal diabetes has been noted both by Allen<sup>1</sup> and Miller, Hurwitz, and Kuder.<sup>2</sup> Miller<sup>3</sup> has also shown that the birth weight of the infant was increased even though the onset of maternal diabetes was delayed until the fifth and sixth decades of life. In Table III are presented data taken from the latter study. The statistics are the result of an investigation into the birth weight of infants born to women who were admitted to the New Haven Hospital with a history of having had an onset of diabetes after they had reached 40 years of age. No infants were included in the study unless they had been born in the New Haven Hospital. The data were few, since the chances were small that a woman would enter the New Haven Hospital with an onset of diabetes after 40 years of age and would have been delivered in the same hospital several years before. No infant who weighed less than 2,500 grams at birth or who was a twin was included. In spite of the small number of births obtainable it is thought that the results are of considerable significance. Three of the twenty-two infants reported in Table III weighed over 5 kg. at birth; six weighed over 4.5 kg. and fifteen weighed 4.0 kg. or more. The incidence of infants in the various weight groups are approximately 200, twenty-seven, and seven times greater, respectively, than the expected ratios for normal newborn infants in the same birth weight categories.<sup>5, 6</sup> The average birth weight of the twenty-two infants in Table III is significantly higher than that of a control group studied in the same hospital.<sup>3</sup>

TABLE III. BIRTH WEIGHT OF TWENTY-TWO INFANTS BORN TO SIXTEEN WOMEN DEVELOPING DIABETES IN THE FIFTH AND SIXTH DECADES

YEARS BEFORE ONSET OF MATERNAL DIABETES			
20-16 YR.	15-11 YR.	10-6 YR.	5-1 YR.
BIRTH WEIGHT (KG.)			
3.0	3.6	4.0	4.2
3.2	3.7	4.1	4.7
3.2	4.0	4.3	5.5
3.4	4.0	4.6	
3.6	4.1	4.7	
	4.2	5.2	
	4.4		
	5.5		

From the case histories of the mothers of the infants whose birth weights are listed in Table III it was possible to be reasonably sure that the infants were born before the onset of diabetes in their mothers. Information concerning the presence or absence of glycosuria was available on the mothers' histories in twenty of the twenty-two pregnancies. Reducing substances were found in the urine of only three mothers during their pregnancies. In the first of these, the fasting blood sugar was 87 mg. per 100 c.c. of blood, and in the second, 89, 94, and 112 mg. The third mother had three urinalyses for sugar during her preg-

nancy and reducing substances were found in only one specimen. None of the sixteen mothers had signs or symptoms of diabetes at any time during the twenty-two pregnancies.

#### ANATOMIC CHANGES IN THE VISCERA AND GLANDS OF INTERNAL SECRETION

Two striking visceral changes have been described in some of the infants born to diabetic mothers; these are an increased size and weight of the heart and an excessive extramedullary erythropoiesis. Both of these changes have been observed in infants who have been born prior to the onset of maternal diabetes.<sup>7</sup> Hurwitz and Irving<sup>8</sup> were the first to report the presence of cardiac enlargement in an infant born to a diabetic mother. They also observed an increased amount of glycogen in the myocardium, using Best's carmine stain. More extensive studies of the cardiac hypertrophy have since been made by Miller and Wilson<sup>9</sup> and Miller, Johnson, and Durlacher.<sup>10</sup> It appears from their studies that cardiac hypertrophy is seen at post-mortem more frequently in those infants who have a birth weight over 4.0 kg. than in those who weigh less. Their studies likewise show that considerable cardiac enlargement apparently is compatible with the survival of the infant. Equally interesting is the fact that the enlargement of the heart as demonstrated by roentgen examination is not permanent but tends to lessen gradually, so that by the time the infant is 2 months old the heart is usually normal in size and shape. A similar change in the heart of an infant born during the prediabetic period has been reported by Miller.<sup>7</sup> The possibility that the cardiac hypertrophy might account for some of the symptoms of infants born to diabetic mothers was considered by Miller and Wilson, but they were not able to reach any definite conclusions on that point.

The cause of the cardiac hypertrophy is not known. The finding of increased amounts of glycogen in the myocardium as reported by Hurwitz and Irving and since corroborated by others<sup>10</sup> offers a possible lead for future study. The excess glycogen in the myocardium of some infants born to diabetic mothers is not to be considered in the same category as that found in cases of von Gierke's disease, in which the glycogen is fixed in the cells probably as a result of failure of the enzyme systems to liberate it. More likely the increase in cardiac glycogen in infants of diabetic mothers is related to some metabolic disturbance associated with the maternal diabetes as has been described in diabetic rats by Lackey, Bunde, Gill, and Harris.<sup>11</sup>

The extramedullary erythropoiesis in infants born to diabetic mothers, which is most marked in the liver and spleen, is observed in almost all cases studied at post-mortem.<sup>9, 10</sup> Since most of these infants are either stillborn or die within the first four days after birth, it is not known how long the extramedullary erythropoiesis persists. Studies of the peripheral blood and its normoblast content suggest that, as in erythroblastosis fetalis associated with Rh incompatibility, the extramedullary activity is short-lived. The differentiation between the extramedullary erythropoiesis associated with the blood incompatibilities of the mother and fetus and the extramedullary erythropoiesis seen in infants born to diabetic and prediabetic mothers has given some difficulty to clinicians and pathologists in the past. There are differences, however, which permit one to

make the correct diagnosis in most instances. The infant born to a diabetic mother or prediabetic mother does not become anemic or develop marked jaundice.<sup>10</sup> Macklin has pointed out that the amount of hemosiderin in the livers of infants born to diabetic mothers is small as contrasted to the large amount seen in infants with Rh incompatibilities in whom considerable hemolysis has occurred.<sup>12</sup> Whenever excessive erythropoiesis is encountered in the newborn infant, red blood cell counts, tests for hemosiderin in the tissues, along with the appropriate tests for blood group incompatibility and tests for congenital syphilis are necessary.

Several of the glands of internal secretion have shown anatomic changes, the significance of which is not clear. Hyperplasia of the islands of Langerhans has been known to occur in some of the infants of diabetic mothers since Dubreuil and Anderodias made their report in 1920.<sup>13</sup> It has recently been shown that similar changes in the islet tissue are to be found in infants born to prediabetic mothers<sup>7</sup> and in infants with erythroblastosis fetalis associated with blood group incompatibility.<sup>14, 15</sup> It has also been shown that occasionally there is an increase in the size and weight of the adrenal glands in infants born to diabetic and prediabetic mothers.<sup>7, 16</sup> A similar finding has been reported by Sarason<sup>16</sup> in some infants with erythroblastosis fetalis. An increase in the amount of eosinophilic elements in the anterior pituitary gland has been shown to be present in infants born to diabetic and prediabetic mothers.<sup>7, 17-19</sup> Also, a considerable hyperplasia of the female sex organs has been described.<sup>20, 21</sup>

The information concerning the anatomic changes in infants born to diabetic mothers is incomplete. No systematic examination of the material has yet been made either as to the incidence of the various changes or their possible interrelationships. Sufficient facts are available to demonstrate that the anatomic changes seen in infants born to diabetic and prediabetic mothers are not specific and that there is a surprising degree of similarity between this group of infants and those with erythroblastosis fetalis associated with Rh incompatibility.<sup>10</sup>

One further anatomic change to be noted is the high incidence of infants born to diabetic mothers who exhibit congenital malformations.<sup>22-24</sup> In nineteen consecutive autopsies on infants born to diabetic mothers, six infants were found in whom there were one or more malformations. These six in addition to one other who survived (Case 7) are listed in Table IV. The anomalies reported in Table IV were reviewed by Dr. George W. Corner of The Carnegie Institute of Embryology. It was his opinion that in all instances the malformations were present before the end of the third month of gestation.<sup>25</sup> The significance of

TABLE IV. CONGENITAL ANOMALIES IN SEVEN INFANTS BORN TO DIABETIC MOTHERS

- 
- |   |
|---|
| 1. Harelip; agenesis of gall bladder; bicornate and septate vagina; hypoplasia of right humerus and femur; agenesis of left femur and fibula; syndactylism; agenesis 12th thoracic vertebra and ribs; sacralization 4th and 5th lumbar vertebrae and fusion of the coccygeal segments |
| 2. Double left ureter with hydronephrosis and hydroureter   |
| 3. Cor biventriolare; hypoplasia of aorta   |
| 4. Bicuspid pulmonary valve   |
| 5. Anencephaly  |
| 6. Agenesis of bladder; agenesis of kidneys; incomplete development of ureters  |
| 7. Persistent pupillary membranes   |
-

these observations is not known but needs to be considered in view of the growing interest in the etiology of congenital anomalies.

#### ETIOLOGICAL FACTORS

During the past few years there has been an increasing tendency to think of the various phenomena observed in infants born to diabetic mothers in terms of some endocrine disturbance. The increasing knowledge that carbohydrate metabolism is vitally affected by the anterior pituitary gland and the adrenal cortex, as well as by the islands of Langerhans, has naturally focused attention on the possible role of the many hormones secreted by these glands as factors in the etiology of the changes seen in these infants. The excessive birth weight of infants born to diabetic mothers has caused many investigators to speculate that the growth hormone of the anterior pituitary might be not only diabetogenic for the mother but growth-promoting for the fetus. In support of this theory is some experimental work by Young, who showed that the injection into puppies of crude pituitary extract in excess of the amount required to produce diabetes in adult dogs caused an increase in growth rate in the puppies.<sup>26</sup> It is also interesting to consider that the splanchnomegaly seen in infants born to diabetic and prediabetic mothers bears some resemblance to that seen in patients with acromegaly. Cushing and Davidoff<sup>27</sup> described marked cardiac hypertrophy without evidence of arteriosclerosis, generalized enlargement of the adrenal cortex with adenomatous changes and hyperplasia of the islands of Langerhans besides an enlargement of the liver and spleen in patients with acromegaly.

The possible role of some hormonal imbalance as a cause for the high fetal and neonatal mortality rate has been the object of several studies carried out by White and other workers in Dr. Joslin's clinic and by Smith, Smith, and Hurwitz.<sup>28</sup> The latter conclude from their investigations that there is a deficiency in the production of steroid hormones by the placenta during diabetes, which causes fetal death. They have suggested large doses of diethylstilbesterol beginning about the sixteenth week of pregnancy in order to counteract the lagging production of estrogen which apparently occurs in the latter part of some diabetic pregnancies. For similar reasons White and Hunt<sup>29</sup> have tried replacement therapy, using estrogen and progesterone in the last half of pregnancies complicated by diabetes, and reported marked success in lowering the number of fetal deaths. It is too early to judge whether or not the replacement therapy employed by the investigators mentioned is going to be uniformly successful in reducing the high mortality among the offspring of diabetic mothers. More studies will be needed before this treatment can be considered to have passed the experimental stage.

#### REFERENCES

1. Allen, E.: *Am. J. Obst. & Gynec.* 38: 982, 1939.
2. Miller, H. C., Hurwitz, D., and Kuder, K.: *J. A. M. A.* 124: 271, 1944.
3. Miller, H. C.: *New England J. Med.* 233: 376, 1945.
4. Herzstein, J., and Dolger, H.: *Am. J. Obst. & Gynec.* 51: 420, 1946.
5. Casagrande, J.: *Am. J. Obst. & Gynec.* 37: 1028, 1939.
6. Koff, A. K., and Potter, E. L.: *Am. J. Obst. & Gynec.* 38: 412, 1939.
7. Miller, H. C.: *Am. J. M. Sc.* 209: 447, 1945.
8. Hurwitz, D., and Irving, F. C.: *Am. J. M. Sc.* 194: 85, 1937.

9. Miller, H. C., and Wilson, H. M.: J. PEDIAT. 23: 251, 1943.
10. Miller, H. C., Johnson, R. D., and Durlacher, S. H.: J. PEDIAT. 24: 603, 1944.
11. Lackey, R. W., Bunde, C. A., Gill, A. J., and Harris, L. C.: Proc. Soc. Biol. & Med. 57: 191, 1944.
12. Macklin, M. T.: J. PEDIAT. 25: 533, 1944.
13. Dubreuil, G., and Anderodias, J.: Compt. rend. Soc. de. biol. 2: 1490, 1920.
14. Liebegott, G.: Beitr. z. path. Anat. u. z. allg. Path. 101: 319, 1938.
15. Potter, E. L., Seckel, H. P. G., and Stryker, W. A.: Arch. Path. 31: 467, 1941.
16. Sarason, E. L.: Arch. Int. Med. 71: 702, 1943.
17. Schretter, G., and Nevinny, H.: Arch. f. Gynäk. 143: 465, 1930.
18. Bauer, J. T., and Royster, H. A.: Bull. Ayer Clin. Lab., Pennsylvania Hosp. 3: 109, 1937.
19. Okkels, H., and Brandstap, E.: Acta path. et microbiol. Scandinav. 15: 268, 1938.
20. Smyth, F. S., and Olney, M. W.: J. PEDIAT. 13: 772, 1938.
21. Benner, M. C.: Arch. Path. 32: 818, 1941.
22. Burns, H. H. F.: J. Obst. & Gynec. Brit. Emp. 48: 707, 1941.
23. Lawrence, R. D., and Oakley, W.: Quart. J. Med. 11: 45, 1942.
24. White, P., Titus, R. S., Joslin, E. P., and Hunt, H.: Am. J. M. Sc. 198: 482, 1939.
25. Corner, G. W.: Personal Communication.
26. Young, F. G.: Brit. M. J. 2: 897, 1941.
27. Cushing, H., and Davidoff, L. M.: Monographs Rockefeller Institute for Medical Research 22: 1927.
28. Smith, O. W., Smith, G. V. S., and Hurwitz, D.: Am. J. Obst. & Gynec. 51: 411, 1946.
29. White, P., and Hunt, H.: J. Clin. Endocrinol. 3: 500, 1943.



## KERNICTERUS IN ERYTHROBLASTOSIS FETALIS

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THE diagnosis of erythroblastosis fetalis has been made at the New Haven Hospital between 1928 and October, 1945, in the cases of seventy-four infants. Twenty-seven deaths have occurred; there have been twenty-three autopsies. Four surviving members of the series show mental retardation. In an analysis of these cases it was found that a large proportion of the deaths occurred in a characteristic manner and that clinicopathologic correlations of considerable interest existed.

In thirteen of twenty-seven deaths the clinical course has been some variant of the following general pattern. An infant, jaundiced within the first three days of life, with a degree of icterus varying from slight to extreme, displays drowsiness or lethargy and may show mild generalized rigidity or a tendency to assume an opisthotonic position, especially when disturbed. Convulsive twitches or spasms occur less frequently than the signs just noted. The infant takes feedings poorly and may vomit. Edema or a sclerema-like condition of the subcutaneous tissue is present at birth or may develop later. Some time between the second and fifth days of life the condition of the infant becomes very alarming. The respirations are found to be irregular or gasping and the child is cyanotic and in peripheral vascular collapse. Examination of the chest discloses râles and rhonchi throughout the lungs. There may be a systolic murmur in the heart which has not been heard on a previous examination. There may soon appear a discharge of bloody froth or mucus from the upper respiratory tract. Death invariably supervenes in a matter of a few minutes or a few hours.

The occurrence of these signs and symptoms marks a group of fatal cases of erythroblastosis fetalis in all of which kernicterus was present at autopsy. The pulmonary lesion which appeared to account for the respiratory signs was focal hemorrhages. These hemorrhages occur into alveoli and give rise to hemorrhagic foci which are generally seen macroscopically as well as microscopically. There may be very extensive involvement of lung or portions of lung in this process. Table I shows that signs relating to the respiratory system were more frequently seen in these babies than those signs suggesting brain injury. In three infants who showed both lesions at autopsy, there was no note made of signs of central nervous system disorder other than gasping and irregularity of respirations; these may well indicate a brain lesion. Of thirteen babies with focal pulmonary hemorrhages twelve had kernicterus, and the other (Case 15) had a diffuse discoloration of cerebral tissue with yellow pigment without localization in the basal nuclei. There was widespread necrobiosis. Durlacher<sup>1</sup> states that pulmonary hemorrhages of the type encountered in these cases may occur in babies with respiratory difficulties con-

sequent upon intracranial hemorrhage in the newborn period. We and others<sup>2, 3</sup> have seen a predilection for involvement of the medullary as well as the basal nuclei in kernicterus: it may be that this involvement brings about disturbed respiratory dynamics which, with the familiar increase in bleeding tendency<sup>4</sup> in erythroblastosis fetalis, result in pulmonary hemorrhagic phenomena.

The specificity of drowsiness, opisthotonos, rigidity, and motor hyperirritability or dyskinesia as signs of kernicterus is suggested by the fact that of the surviving children in this series who had any of these signs other than drowsiness during the acute phase of erythroblastosis fetalis, all four are mentally retarded and present some motor disability, presumably the sequel of kernicterus. Two other infants with such signs, who survived the acute phase of the illness with severe neurological sequelae, died at 5 months and at 3 years of age, and are included among the patients dead with kernicterus listed in Table I. In both of these children autopsy showed extensive destruction of the basal ganglia.

TABLE I. CLINICAL MANIFESTATIONS IN SEVENTY-TWO CASES OF ERYTHROBLASTOSIS FETALIS

	DROWSINESS LETHARGY	SPASTICITY RIGIDITY	OPISTHOTONOS	CONVULSIVE DISORDER	GASPING IRREGULARITY	HALES RHONCHI	BLOODY DISCHARGE FROM RESPIRATORY TRACT	DEVELOPED SYSTOLIC MURMUR	EDEMA
A. Cases with kernicterus									
Dead (16 cases)	7	5	6	4	12	12	9	7	6
Living (4 cases)	3	1	2	2	0	0	0	0	0
B. Cases without kernicterus									
Dead (9 cases)	2*	2*	0	0	3†	2†	0	0	5†
Living (43 cases)	5	0	0	0	0	0	0	0	6

\*Includes Case 34, not autopsied.

†Includes two cases of hydrops fetalis.

The autopsied cases in which kernicterus was not present form a heterogeneous group (Table VIII) and deserve individual mention:

In Cases 11 and 25, hydrops fetalis was present. Both babies died on the first day of life.

In Case 22 the infant was born pale and gasping, with mild icterus, and shortly developed petechiae of the face. Death occurred at 4 hours, while transfusion was being attempted. Autopsy disclosed extensive involvement of the brain in petechial hemorrhages. Erythropoiesis in other organs was marked.

In Case 15 the baby developed icterus and anemia extremely rapidly after birth, with marked enlargement of the liver and spleen. Death occurred at 25 hours. The brain showed the diffuse discoloration already described and pulmonary hemorrhages were present. Two siblings of this infant subsequently recovered from erythroblastosis fetalis of which the outstanding signs were icterus, splenomegaly, and anemia.

Case 29 has been mentioned previously (Miller,<sup>5</sup> Case 8, Table IV). Rh incompatibility was present. The baby was cyanotic at birth and remained so for the duration of life. Blood sugar on the first day was 17 mg. per cent. Jaundice became manifest on the second day shortly before the child died. Death appeared to be due to progressive heart failure. At autopsy the liver was large, the spleen of normal size. Erythropoiesis was moderately increased in the liver. There was eosinophilia in the pars anterior of an enlarged pituitary gland, increased glycogen in the heart (1.6 per cent), and generalized splanchnomegaly. No anti-Rh substance was detected in the mother's serum. The mother developed diabetes mellitus about a year after the termination of this pregnancy. These circumstances make it seem very doubtful that death was due to erythroblastosis fetalis.

Case 41 was that of a premature infant (birth weight 2,250 Gm.) in whom icterus was first noted on the fifth day, although it may have been present earlier. The baby received clyses of saline after the second day in accordance with the usual standards for the management of premature infants on our service. Weight gain was rapid, and on the tenth day massive edema was apparent. Death occurred on the twelfth day apparently from heart failure. At autopsy the liver and spleen were of normal size, without any increase in erythropoiesis. The brain was normal. There was marked cardiac hypertrophy (32 grams). Although Rh incompatibility was demonstrated, no antibody was found in the mother's serum, and furthermore the infant was the result of the first pregnancy of a mother who had had no previous transfusion. These considerations seriously challenge the diagnosis of erythroblastosis fetalis.

(Cases 29 and 41 will not be further considered and do not appear in any of the tables, since the diagnosis of erythroblastosis fetalis is in doubt.)

In Case 39 death occurred on the twentieth day of life shortly after transfer from a neighboring community and before therapy could be initiated. The red blood cell count on entry was 600,000 cells per cubic millimeter. A sibling later recovered from erythroblastosis fetalis following transfusion.

In Case 7 (birth weight 1,700 Gm.) icterus developed on the first day and then anemia appeared, for which transfusion was necessary. Death occurred at 1 month from hydrocephalus complicating subdural hematoma. The only residual at post-mortem of the acute erythroblastosis fetalis was a large liver with periportal fibrosis (Miller's<sup>5</sup> Case 12, Table IV).

In four cases permission for autopsy was not granted. In Case 4, which has been discussed in detail by Miller<sup>6</sup> (Case 4), the diagnosis of kernicterus is certain on clinical grounds. In Case 34 death occurred suddenly on the fourteenth day, and appeared to follow the aspiration of vomitus. A sibling of this baby later died of kernicterus (Case 74). In Cases 52 and 63 death was very sudden, in both instances on the second day. Case 52 resembled Case 22 in certain of the clinical manifestations (anemia, petechiae).

If we exclude from consideration those cases where death was avoidable (Case 39) or we were reasonably certain not due to acute erythroblastosis fetalis (Cases 7, 29, and 41), it is seen that an unfavorable outcome (death or survival with mental retardation) has been associated with kernicterus in 20

of 27 cases in this series. This high incidence of kernicterus is in accord with recently reported<sup>2</sup> observations elsewhere. In attempting to gain insight into the mechanism of occurrence of this important complication of erythroblastosis fetalis we have tried to correlate kernicterus with the other findings of the disease.

## CLINICOPATHOLOGIC CONSIDERATIONS

It has been recognized<sup>4</sup> that lack of red cells is rarely the cause of death in erythroblastosis fetalis. In the babies who developed kernicterus in this series the minimum red blood cell count was above 1.8 million in all, and above 3.0 million in many for the duration of the illness. These patients showed no greater tendency to develop anemia than the group that recovered and in several of the cases of kernicterus anemia was conspicuous only by its relative absence. More noteworthy than the lack of anemia in many of these babies with cerebral involvement, however, was the comparative lack of signs of hematological distress. The size of the spleen may be taken as measuring roughly the demands placed upon the organ in removal of products of red blood cell destruction.<sup>7</sup> It is commonly described in units of fingerbreadths in the living infant. About one-quarter (10) of the surviving cases (43) in this

TABLE II. DETAILS OF CLINICAL AND ANATOMIC FINDINGS IN AUTOPSED CASES

CASE	ICTERUS	BODY WT. (GM.)	HEART (GM.)	LIVER (GM.)	SPLEEN (GM.)	FINGER- BREADTH	EXTRA- MEDULLARY ERYTHRO- POIESIS
A. Cases with kernicterus							
1	2nd day	3,200	30	150	14	1	Slight
5	1st day	2,095	16	110	28	2	Marked
9	3rd day	3,155	35	140	25	2	Slight
33	Birth	3,100	20	140	22	2	Moderate
47	1st day	3,360	18	145	23	2	Normal
48	1st day	3,940	21	190	23	1	Slight
56	1st day	2,410	22	85	10	1	Slight
64	Birth	2,600	17	120	8	1	Slight
74	Birth	2,650	23	180	26	1	Marked
65	1st day	3,575	27	150	27	2	Slight
2	3rd day	2,975	24.5	100	13	1	Slight
75	1st day	2,675	15	110	11	1	Slight
73	1st day	3,800	22	200	32	2	Moderate
B. Cases without kernicterus							
11	Birth					30	Marked
15	3 hours	4,304	35	338	45	3	Marked
22	Birth	3,147	22	203	25	2	Marked
25	Birth	4,700	60	320	47	3	Marked
C. Probably not erythroblastosis fetalis							
29	1st day	4,725	50	260	12	0	Moderate
41	4th day	2,715	32	100	6	1	Normal

series had spleens recorded as being 3 or more fingerbreadths enlarged. Yet in eleven of twenty babies who developed kernicterus the maximum recorded size of the spleen was 1 fingerbreadth or less and in none of the remainder was the maximum measurement as much as 3 fingerbreadths. Nor is the weight of the organ necessarily outstanding at autopsy, as shown in Table II, where reasonably satisfactory correlation is seen between the weight of the spleen

post mortem and the size in fingerbreadths before death. These striking figures reflect only in part a slight tendency of kernicterus to occur in the smaller infants. The weight range, 3,000 to 4,000 Gm., includes eleven cases of kernicterus and the majority of surviving infants who had 3 fingerbreadths' enlargement of the spleen; both groups are fairly evenly distributed. Table III shows that the probability that no infant in this weight range with kernicterus would be in the group with 3 fingerbreaths enlargement is P less than 0.10. Five of the infants with kernicterus had only a 1 fingerbreadth enlargement. These figures suggest not only that kernicterus is not necessarily associated with marked blood destruction, but also that blood destruction may be generally less in the babies with kernicterus than in an equally large group of *recovered* cases of erythroblastosis fetalis.

TABLE III. RELATION OF SIZE OF SPLEEN TO OUTCOME IN WEIGHT RANGE 3,000-4,000 GM.

	SPLEEN			AVERAGE WEIGHT
	1 FINGER-BREADTH OR LESS	2 FINGER-BREADTHS	3 FINGER-BREADTHS OR MORE	
Kernicterus (11 cases)	5	6	0	3,543 ± 191 Gm.
Recovered (29 cases)	15	5	9*	3,427 ± 261 Gm.
Total	20	11	9	
Kernicterus expected	5.5	3.0	2.5	$X^2 = 5.5 \quad P < 0.10$

\*Weight range 3,000-3,995 Gm. Average weight 3,458 ± 316 Gm.

Extramedullary erythropoiesis is a second index of the reaction of the hematopoietic system to injury. Taking the liver as a representative organ, we observed considerable variation in erythropoiesis in the cases with kernicterus (Table III). The majority showed only minimal increases. In the few autopsied cases in which kernicterus was not found, erythropoiesis was generally much more marked. There is some hint that the most marked extramedullary erythropoiesis was likely to be seen in the infants in whom icterus was present at birth or developed very soon thereafter.

However, the time of onset of icterus seems to have no prognostic significance in this series. As shown in Table IV neither the outcome in general nor the incidence of kernicterus is related to the time of onset of jaundice, whether before birth, during the first twenty-four hours, or later. Nor were we able to relate the occurrence of kernicterus to the intensity of icterus. Many extremely jaundiced babies recovered completely, whereas certain infants with mild or only moderate degrees of icterus developed kernicterus.

TABLE IV. RELATION OF OUTCOME IN ERYTHROBLASTOSIS FETALIS TO TIME OF ONSET OF ICTERUS

	ICTERUS			
	AT BIRTH	IN LESS THAN 24 HR.	IN MORE THAN 24 HR.	NEVER
Total	25 cases	24 cases	17 cases	6 cases
Recovered	17	9	12	5
Dead	8 (32%)	15 (62%)	5 (29%)	1
Kernicterus (%)	5 (20%)	10 (42%)	5 (29%)	0

TABLE V. RELATION OF KERNICTERUS TO THE OCCURRENCE OF EDEMA

TIME OF ONSET	BIRTH WEIGHT (GM.)	TIME OF ONSET	BIRTH WEIGHT (GM.)
<i>Recovered patients (43 cases)</i>		<i>Cases with kernicterus (20 cases)</i>	
2nd day	4,500	2nd day	2,055 (Case 5)
3 hours	4,125	Birth	3,100 (Case 33)
Birth	3,610	1th day	3,575 (Case 47)
Birth	4,650	5th day	2,360 (Case 56)
1st day	3,600	5th day	3,200 (Case 65)
3rd day	3,600	1st day	3,800 (Case 73)

Edema was about twice as common in the cases developing kernicterus as in the group of recovered cases and was mild in both groups (Table V). In four of six patients with kernicterus, edema did not appear until within twenty-four hours of death, whereas, in four of the six edematous patients who recovered, the edema was established by the end of the first day.

We found kernicterus somewhat more likely to occur in the smaller babies. Table VI, which relates birth weight to the occurrence of kernicterus or survival, shows that a birth weight of 3,000 Gm. divides the group with kernicterus into 50 percentile partitions and the group of recovered patients into 25 and 75 percentile partitions. This result has no statistical significance ( $P < 0.20$ ); but it is noteworthy that of the babies who developed edema as a manifestation of acute erythroblastosis fetalis and recovered, all weighed 3,600 Gm. or more at birth (Table V), while of those edematous babies developing kernicterus, only one weighed more than 3,600 Gm. (Case 73).

In no case of kernicterus was there anatomic evidence of such blocking of terminal blood capillaries with cellular debris as Diamond and Denton<sup>7</sup> and Liber<sup>8</sup> suggest may contribute to an unfavorable outcome in erythroblastosis fetalis. In Case 22 and in the stillborn hydropic sibling of one of our patients who recovered, on the other hand, there was a diffuse petechial hemorrhagic injury to the brain with evidence of attempted repair, which might be interpreted as resulting from the plugging of small blood vessels by masses of nucleated red blood cells, which were present in abundance and were larger than the normal cell. In neither of these cases was kernicterus seen, whereas in certain of the brains in which kernicterus was intense in gross sections, no microscopic abnormality whatever was encountered. Necrobiosis and other changes described elsewhere<sup>2</sup> as characteristic of kernicterus were absent, as well as any evidence of vascular injury.

TABLE VI. RELATION OF OCCURRENCE OF KERNICTERUS TO BIRTH WEIGHT

	BIRTH WEIGHT				
	BELOW 2,500 GM.	2,500 TO 3,500 GM.	ABOVE 3,500 GM.	BELOW 3,000 GM.	ABOVE 3,000 GM.
Kernicterus	4	8	8	9	11
Living	3	25	15	11	32

Except for the replacement of red blood cells in infants where anemia was a real threat to life, the use of blood transfusion in therapy of erythroblastosis fetalis has not appeared to affect the outcome, as shown in Table VII.

TABLE VII. RELATION OF TRANSFUSION TO OUTCOME IN ERYTHROBLASTOSIS FETALIS

DONOR	TRANSFUSED WITHIN FIRST FIVE DAYS OF LIFE			TRANSFUSED FIRST DAY		
	LIVING	DEAD	KERNIC-TERUS	LIVING	DEAD	KERNIC-TERUS
Father	4	3	2	2	1*	0
Untyped	12	4	3	3	1†	0
Rh negative	10	5	4	2	4	3

\*Case 15.

†Case 25.

Three cases of kernicterus were transfused only when moribund, one with untyped, and two with Rh negative blood; they are excluded from consideration.

Consideration is limited to transfusions given during the first five days of life, since it is within that period that the great majority of deaths from acute erythroblastosis fetalis occur (Table VIII). No significant or striking correlation of outcome with the Rh type of the blood used nor time of administration was found when this five-day period or shorter periods were considered, until the effect of transfusions given within the first day was noted. It is seen that no infant who received Rh-positive blood on the first day of life died with kernicterus. This suggested superiority of Rh-positive blood given within the first twenty-four hours in preventing kernicterus is by no means statistically significant, but it represents the most striking deviation from the general finding that the type of blood used in therapy had no effect on the outcome.

TABLE VIII. TIME OF DEATH IN ACUTE ERYTHROBLASTOSIS FETALIS

1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	LATER
	Case 63				
	Case 52				
	Case 15		K		
Case 22	K	K	K	K	
Case 11	K	K	K	K	Case 34—14 days
Case 25	K	K	K	K	K—8 days

K = kernicterus.

## DISCUSSION

Early investigators of the Rh factor were able to demonstrate it only in the red blood cell.<sup>9, 10</sup> It was therefore assumed that the signs and lesions of erythroblastosis fetalis were consequent upon injury to the red cell alone and that hemoclasia was the dominant pathogenetic process.<sup>7, 11</sup> But in infants with kernicterus we have found no uniformly marked anemia, icterus, or other signs of blood destruction, neither clinically nor at post-mortem examination; nor have we found anatomic evidence that blood destruction is involved in the production of kernicterus except as it may lead to an increase in serum bilirubin. Darrow<sup>12</sup> also has been unable to correlate brain damage with severity of clinical signs. Boorman and Dodd,<sup>13</sup> moreover, have recently demonstrated the Rh factor in a variety of tissues, and suggest that prior attempts to demonstrate the factor in body fluids or in aqueous extracts of organs may have been

fruitless because the factor is not very soluble in water. These authors consider it likely that the Rh factor is as general a characteristic of tissues as the A and B factors. It seems plausible that any tissue where Rh specificity is a protoplasmic characteristic should be held susceptible to injury by Rh antibody.

Kernicterus is not yet, however, clearly accounted for in terms of an antigen-antibody reaction. We do not know whether it represents a primary nerve cell injury, with secondary pigmentation and later morphologic change, or whether it is primarily a vascular disease with secondary pigment deposition and nerve cell injury. Vascular endothelial trauma might come from direct assault by the Rh antibody, or from the by-products of intravascular hemolysis. A primary vascular basis for kernicterus is suggested by the fact that the regions in which the pigment is found are those in which asphyxia and anoxia generally have their most devastating effects.<sup>14, 15</sup> This has been considered the probable result of the fact that these are brain areas which have a relatively poor blood supply,<sup>15</sup> and may therefore be more susceptible to injury when generalized disturbances in blood supply or oxygen transport occur. Edema in erythroblastosis fetalis may well reflect a generalized injury to vascular endothelium, which results in increased capillary permeability when tissue anoxia occurs. The high incidence of kernicterus in smaller babies with edema suggests that edema and kernicterus may be etiologically related.

In experimental studies relating to the blood-brain barrier Broman<sup>16</sup> concluded that vascular injury was prerequisite to staining of injured cerebral tissue by trypan blue, which bilirubin is said<sup>17</sup> to resemble in its behavior toward the cerebral vascular endothelium. Broman felt that nerve cell injury alone did not give rise to altered reactivity to trypan blue. King,<sup>18</sup> on the other hand, holds brain tissue injury essential to this altered reactivity, and suggests that vascular changes may follow nerve tissue injury in a manner analogous to the chemotactic phenomena of inflammation. Certain antibodies<sup>17</sup> are known to diffuse readily across the hematoencephalic barrier, and in the event that brain cells are shown to be Rh positive, then injury of such cells by Rh antibody becomes a readily conceivable possibility.

Immaturity of cerebral or cerebrovascular tissues may play an etiological role in kernicterus, as suggested by Table VI. There is experimental confirmation of this notion. Friedemann<sup>17</sup> found that certain substances permeated the cerebral vascular endothelium of young mice which did not cross the endothelium of older animals. Frohlich and Mirsky<sup>19</sup> produced convulsions in young rats by the administration of bilirubin, but not in older rats. We and others<sup>20</sup> have observed kernicterus in premature infants, with and without sepsis, where the role of isoimmunization could be reasonably excluded. However, almost one-half (8) of our patients with kernicterus weighed over 3,500 Gm. at birth, which hardly suggests immaturity. Moreover, in a recent review of kernicterus, Docter<sup>3</sup> concluded that, except where erythroblastosis fetalis was also present, kernicterus has never been seen complicating congenital atresia of the bile ducts, which is the principal condition besides erythroblastosis fetalis which may produce intense jaundice in the newborn



period. While immaturity may well play some part in the causation of kernicterus, we feel that it does not by any means play the dominant role.

Even if kernicterus proves to be the result of local injury to Rh-positive tissues by anti-Rh substance, there is no explanation for the fact that the infants' Rh-positive red blood cells do not protect the brain from this local injury, nor any accounting of the possibility that in infants with kernicterus blood destruction may be moderated in comparison with a large group of recovered cases. It may happen in certain infants with erythroblastosis fetalis that the red cells have diminished capacity to absorb Rh antibody, that the red cells are resistant to destruction by antibody, or that the antibody has an equal or greater attraction for other tissues. Macklin<sup>21</sup> has proposed that in certain instances sensitization of the mother may be initiated by red cells with an Rh-antigenic structure characteristic of an earlier stage in the development of the fetal red cell than is represented by the fetal cell at term or the adult red cell. Antibody resulting from contact with such cells might have a great affinity for fetal tissues other than the erythrocyte. Alternative speculations are that ante-partum exposure of fetal erythropoietic tissues to small quantities of anti-Rh substance might so alter the mechanism for elaboration of Rh factor that certain erythrocytes at term are unreactive to maternal antibody, or that fetal placental tissue itself, with an Rh-antigenic structure more or less complex than that of the red blood cell, may in certain cases alter the specificity of maternal sensitization.

The possible role of "blocking antibody" in moderating blood destruction in infants with kernicterus is not clear at the present time. Wiener<sup>22</sup> reports that the presence of such antibody may give a false Rh-negative result in the typing of certain erythroblastotic infants and also confuse the picture of Rh sensitization in the mother when special tests<sup>23</sup> are not done. It is conceivable that "blocking" of fetal cells might turn the usual type of antibody to other tissues. However, in Case 56 of our series careful tests for blocking antibody were done, and none reported, while the titer of ordinary antibody was 1:16. The pathologic signs of blood destruction were minimal in this infant (Table II), and this was true of the clinical signs as well (icterus index 40, no normoblastemia, hemoglobin 9 Gm.). Kernicterus was marked in gross sections, but no microscopic abnormality was discovered in the brain. This case makes it appear that the presence of blocking antibody is not essential to any sparing of signs of blood destruction in an infant with kernicterus.

The common delay after birth in development of signs of erythroblastosis fetalis suggests that factors associated with delivery may be of great importance in the study of the disease. The fact that kernicterus is very common in infants who develop icterus only after birth and the fact that certain of the infants dying of kernicterus have little or no sign of long-standing injury due to maternal antibody suggest further that these factors associated with delivery may be of such significance as to account for kernicterus in some babies. It should be emphasized that these factors may also give rise to an illness in which blood destruction is marked and recovery takes place notwithstanding.

This hemoclastic type of erythroblastosis fetal<sup>is</sup>, as indicated by the size of the spleen, bears no more relation to the time of onset of icterus than does kernicterus.

It is well known that the act of delivery of an erythroblastotic infant has a very significant effect on the mother, since her production of antibody is stimulated at this time, and her titer of antibody becomes higher in the weeks post partum than it was before delivery.<sup>24</sup> It seems likely<sup>25</sup> that this increase in maternal antibody titer after delivery is due to stresses placed upon the placental barrier during labor which result in the entrance of fetal blood cells, with or without placental tissue, into the maternal circulatory system. The period of the second and early third stages of labor, which require that the placenta adjust to decreasing uterine volume and surface, may be a critical period in determining the amount of fetal antigen to which the mother is exposed. It is not unreasonable to suppose that if fetal cells can reach the maternal circulation during this period, then maternal serum may by a similar process attain the fetal blood stream. If such intrapartum transfer of antibody from mother to fetus dominates the development of erythroblastosis fetal<sup>is</sup> in a given infant, then a delay of several hours after delivery in development of signs of the disease would be understood. If kernicterus were the outcome, a paucity of signs of long-term injury to fetal tissues (such as organ hypertrophy or marked erythropoiesis) might likewise be accounted for.

While such speculative considerations as these may explain the occurrence of erythroblastosis fetal<sup>is</sup> in an infant who appears normal at birth, they do not help us to understand why preferential blood destruction does not protect babies with kernicterus. A further explanation in terms of antigen-antibody reactivity or other factors is necessary. It is conceivable that the rate of delivery of antibody from mother to fetus might play some role, the more rapid rate allowing general distribution of antibody to fetal tissues before the action of the Rh-positive erythrocyte in sparing tissue damage might become effective. Our data on the course of labor do not permit us to examine this possibility, nor is there certainty that factors determining the amount and rate of any intrapartum transfer of antibody will be capable of evaluation.

If future studies or experimental work confirm the suggestion that intrapartum transfer of antibody plays an important role in the development of erythroblastosis fetal<sup>is</sup> in the infant, it might be found that the transfer of antibody from mother to fetus could be minimized if delivery were accomplished by cesarean section, with rapid securing and ligation of the umbilical cord. Even when pelvic delivery is rapidly effected, there may be placental stresses during the second and early third stages of labor which hold an unpredictable hazard for the infant.

Diamond<sup>20</sup> reports that the obstetrical management of mothers with erythroblastotic babies has already significantly lowered the mortality among the infants. He advises early interruption of pregnancy in the event of a rising anti-Rh titer, as soon as there is a viable fetus for whom mild erythroblastosis fetal<sup>is</sup> superimposed upon prematurity should not prove too great a burden.

Our experience with the relation of kernicterus to the smaller infants suggests that this program has limitations. It may be that some increased factor of safety would accrue if cesarean section were used in effecting the early delivery.

Another possible conclusion based on the foregoing speculations is that early use of Rh-positive blood transfusion might ameliorate the prospects of an infant in whom kernicterus is anticipated by offering a sponge to antibody transferred during delivery. It would be hoped that fresh Rh-positive cells (of appropriate subtype), not exposed to maternal antibody at any time during their development, would have a high affinity for maternal antibody, sparing tissue cells from injury. If the transfused cells had no greater affinity for maternal antibody than the fetal cells, or if they were of no value in fixing circulating antibody, then their use in therapy would be worthless as far as altering the prospect of kernicterus is concerned. But Mollison<sup>26</sup> and others<sup>27</sup> have shown that, even later in erythroblastosis fetalis than the first few hours after birth, Rh-positive cells used in treatment are more rapidly destroyed than Rh-negative cells. The implied continuing presence of available antibody in the infant leads us to consider that *in certain infants* the destruction of transfused Rh-positive cells may be a desirable event, causing the removal of anti-Rh substance from fetal fluids and possibly from loose attachment to fetal tissues. Rh-negative blood is undoubtedly advantageous in the treatment of uncomplicated erythroblastotic anemia<sup>27</sup> or in the treatment of the infant, rare in our experience, in whom blood destruction itself seems to be the main threat to life. But we do not feel that its routine use in the therapy of erythroblastosis fetalis will necessarily lower the incidence of kernicterus, since our results indicate that kernicterus is more likely the result of direct injury to cerebral or cerebrovascular tissues by antibody than the consequence of blood cell destruction.

It cannot be too strongly emphasized that while the conclusion that kernicterus may not be the result of blood destruction seems justified by the observed facts, on the other hand, suggestions as to how kernicterus might be prevented are theoretical, and neither proved nor rigorously tested. Analysis of other large series of cases of erythroblastosis fetalis must be made, testing the reliability of our data before any commitment regarding therapy can be formulated. Our experience, and that of others<sup>12, 28</sup> who have employed early transfusion of Rh-positive blood, suggests that it is not generally harmful to the infants in whom it is used. It may be that only further use can answer the question whether the foregoing theoretical considerations have any basis in fact or any practical application. Diamond<sup>29</sup> would caution very strongly against the use of Rh-positive blood in infants in whom cells sensitized by the so-called blocking antibody may be present. He has found that even *washed* Rh-positive cells may agglutinate in the presence of Rh-positive cells sensitized by blocking antibody. This reaction has been seen *in vitro*, and appears to have been the reason for an unfavorable outcome in at least one case of erythroblastosis fetalis in Diamond's experience. It may be pointed out that if it were possible to obtain an Rh-positive antigen unattached to the red blood cell, this

substance would be preferred to Rh-positive blood as a therapeutic agent since it might neutralize antibody without enhancing hemagglutination or hemolysis.

# SUMMARY

In a series of seventy-two cases of erythroblastosis fetalis there were twenty-five deaths with twenty-one autopsies. Four of the surviving patients have mental retardation. An unfavorable outcome was associated with the clinical or pathologic signs of kernicterus in twenty cases. In twelve cases of kernicterus there were also focal pulmonary hemorrhages and these infants displayed a striking clinical picture, made up variously of drowsiness, spasticity, opisthotonos, signs of motor irritability, respiratory irregularity, pulmonary râles and rhonchi, and bloody discharge from the upper respiratory tract.

Clinical and pathologic features of the cases with kernicterus suggest that blood destruction is not the primary determinant of nuclear damage. The possible roles of immaturity, vascular injury, altered antigen-antibody reactivity, and intrapartum transfer of antibody in the pathogenesis of kernicterus are discussed.

I wish to express my appreciation to Dr. Louis K. Diamond for the performance of many blood tests in this series of patients and for his criticism of this paper.

# REFERENCES

1. Durlacher, S. H.: Personal communication.
2. Zimmerman, H. S., and Yannet, H.: *Am. J. Dis. Child.* 45: 740, 1933.
3. Docter, J. M.: *J. PEDIAT.* 27: 327, 1945.
4. Leonard, M. F.: *J. PEDIAT.* 27: 249, 1945.
5. Miller, H. C., Johnson, R. D., and Durlacher, S. H.: *J. PEDIAT.* 24: 603, 1944.
6. Miller, H. C.: *Yale J. Biol. & Med.* 11: 363, 1939.
7. Diamond, L. K., and Denton, R. L.: *J. A. M. A.* 128: 686, 1945.
8. Liber, A. F.: *J. A. M. A.* 128: 686, 1945.
9. Levine, P., and Katzin, E. M.: *Proc. Soc. Exper. Biol. & Med.* 48: 126, 1941.
10. Wiener, A. S., and Forer, S.: *Proc. Soc. Exper. Biol. & Med.* 47: 215, 1941.
11. Potter, E. L.: *Am. J. Dis. Child.* 68: 32, 1944.
12. Darrow, R. R.: *J. A. M. A.* 127: 1146, 1945.
13. Boorman, K. E., and Dodd, B. E.: *J. Path. & Bact.* 55: 229, 1943.
14. Putnam, T. J., and Alexander, L.: *A. Research Nerv. & Ment. Dis.* 18: 544, 1937.
15. Wolff, H. G.: *A. Research Nerv. & Ment. Dis.* 18: 29, 1937.
16. Broman, T.: *Acta psychiat. et neurol.* 16: 1, 1941.
17. Friedemann, U.: *Physiol. Rev.* 22: 125, 1942.
18. King, L. S.: *A. Research Nerv. & Ment. Dis.* 18: 150, 1937.
19. Frohlich, A., and Mirsky, I. A.: *Proc. Soc. Exper. Biol. & Med.* 50: 25, 1942.
20. Diamond, L. K.: *New England J. Med.* 232: 447, 1945; 232: 475, 1945.
21. Macklin, M. T.: *Am. J. Dis. Child.* 67: 445, 1944.
22. Wiener, A. S.: *J. Lab. & Clin. Med.* 30: 662, 1945.
23. Diamond, L. K., and Abelson, N. M.: *J. Lab. & Clin. Med.* 30: 668, 1945.
24. Boorman, K. E., Dodd, B. E., and Mollison, P. L.: *J. Path. & Bact.* 57: 157, 1945.
25. Wiener, A. S.: *J. Lab. & Clin. Med.* 30: 957, 1945.
26. Mollison, P. L.: *Arch. Dis. Childhood* 18: 161, 1943.
27. Blackfan, K. D., Diamond, L. K., and Leister, C. M.: *Atlas of the Blood in Children*, New York, 1944, Commonwealth Fund, p. 94.
28. Sanford, H. N.: *M. Clin. North America* 30: 75, 1946.
29. Diamond, L. K.: Personal communication.

## THE IMPORTANCE OF CHRONOLOGIC RECORDS IN THE MANAGEMENT OF ALLERGIC CHILDREN

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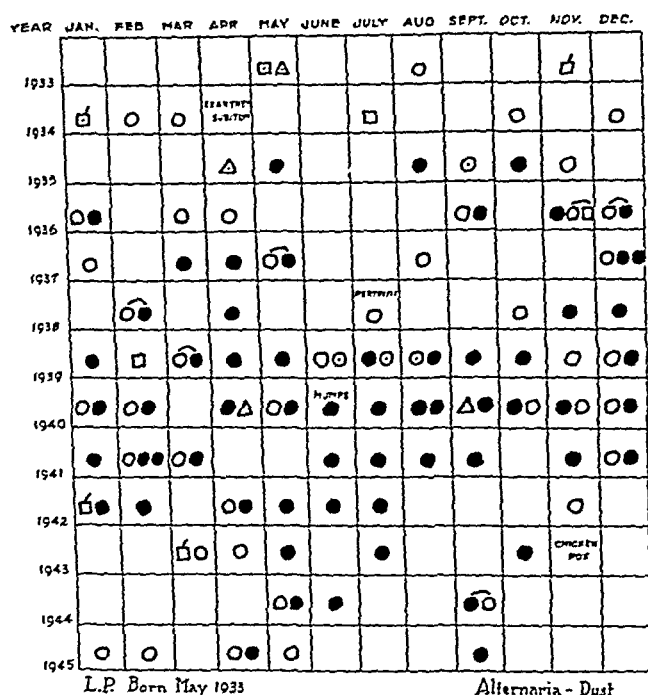
THE importance of accurate histories in the diagnosis and treatment of allergic diseases has been repeatedly emphasized. Stevens pertinently remarks that "An hour's time spent in taking a history is worth more than a hundred skin tests." Once obtained, the items in the history cannot be regarded with the finality of fixed statistical data, but as clues that may need rechecking. The skillful allergist learns to sift the chaff from the wheat in the patient's story long before the skin has been scratched. He has no way, however, of proving or disproving the truth of related episodes, and as every pediatricist who has had to fill out a college entrance blank for one of his wards knows, the authenticity of history recitals from the mother varies inversely with the length of time elapsed and the size of her family. The average history recorded by the fledgling clinical clerk is a gallimaufry of distracted parental memories.

In the field of allergic diagnosis, more perhaps than in other fields of medical diagnosis, chronologic relationships assume great importance. An asthma attack "about six months ago" has little specific significance. Asthma spells occurring from March through October at least point a finger to a possible mold allergy relationship. Rackeman illustrates the importance of the chronologic relations by the story of the schoolboy who had attacks three times a year—"eleven months ago, seven months ago, and five months ago"—a meaningless story until the dates were recorded and it was appreciated that December 21, March 28, and June 12 represented the change from boarding school to a home where there was a cat.

The intimate parent-physician relationship enjoyed by the pediatrician permits him to obtain details missed or confused in a clinical biography written long after their occurrence and the mother of a child, if instructed, will willingly phone the physician's office to report medical incidents at the time of their occurrence. The record of these details may be incorporated on a chronologic sheet in the patient's folder by the physician's secretary or nurse at that time. The mother is much less apt to keep a dependable diary. As the physician adds the details of his house or office calls, a chronologic record is obtained which, on one sheet, will give a graphic visualization of a child's entire medical history.

By the use of arbitrary symbols to express various symptoms or symptom-complexes the secretarial work involved is reduced to a minimum. Symbols are used to express these signs and symptoms: upper respiratory infection, excessive sneezing, hay fever, ambulant asthma, asthma severe enough to con-

fine patient to bed, atopic dermatitis, nonallergic skin disease, styes, digestive upset suggesting allergic component (colic), vomiting, diarrhea, digestive upset of infectious type, nosebleed, enuresis, vaginitis. (No originality is claimed for the characters of symbols used, and many persons with greater artistry or ingenuity may find a more graphic medical shorthand.)



- |                                  |   |
|----------------------------------|---|
| ○ Upper respiratory infection    | □ Colic or abdominal pain of allergic character |
| ○ Hay fever symptoms             | ◻ Colic with vomiting                           |
| ● Asthma                         | ◻ Colic with diarrhea                           |
| △ Skin symptoms-nonallergic      | ∩ Styes   |
| △ Atopic dermatitis or urticaria | N Nosebleed                                     |
| ▽ Enuresis                       | C Canker sores                                  |
| ◻ Digestive upset-nonallergic    | M Migraine                                      |
|                                  | F Unexplained fever                             |

Fig. 1.—Chronologic chart. The year-round incidence of allergic signs is noted in third year of life. The reduced incidence of asthma during the last five years is graphically presented.

By the use of these symbols on a page lined vertically by months, horizontally by years, a ten-year listing of medical incidents may be portrayed on a single page (Fig. 1). Such a chronologic record will, at a glance, show in what months the child's symptoms appear, the frequency of attacks, what sys-

tems are involved, change of shock organ bearing the brunt of allergic attack. Records of this character have frequently shown discrepancies between the family's recollections and the actual incidence of certain symptoms. They refute or confirm the impressions of the effectiveness of methods of treatment.

In the cases of pediatric patients later referred to an allergist who treats adults, transfer of the chronologic records will be of help to the allergist and patient alike and provide a more accurate background for guidance and therapy.

## NONRACHITIC BOWLEGS IN CHILDHOOD

### OSTEOCHONDROSIS DEFORMANS TIBIAE

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IT SEEMS likely that many medical men will continue to consider the childhood condition of bowlegs as almost invariably the result of rickets. They will, therefore, continue to explain the cases in which bowlegs have developed in spite of regular, adequate doses of vitamin D by the unconvincing arguments that assimilation has been faulty or that individual requirements have been excessive. This, as an initial conclusion, should not be accepted by the pediatrician or the orthopedic surgeon until the differential points have been visualized by x-ray. Perhaps the reassertion that the occurrence of nonrachitic bowlegs is surprisingly frequent will serve to emphasize an alternate diagnosis until the syndrome of *osteochondrosis deformans tibiae* or "tibia vara"<sup>3</sup> will also come to mind whenever a case of bowlegs is encountered. Probably very little harm has been done in the past by the assumption that bowlegs always means rickets. Giving more and more cod liver oil in misdirected treatment of nonrachitic bowlegs has certainly caused no injury and the final correction of the deformity can be expected to become an orthopedic procedure in any case. Recognition of the nonrachitic nature of bowlegs would, however, relieve the attending physician, or his predecessor, of the blame for failing to control the advance of rickets which has been rightly classed as a preventable disorder.

The entity *tibia vara* seems to have been first effectively publicized by Blount<sup>3</sup> who made an analysis of the condition in sufficient detail to establish diagnostic features distinguishing it from rickets, dysechondroplasia (Ollier's disease), syphilis, tuberculosis, osteochondritis. The conception of the condition has been further advanced by the observations of Barber<sup>1, 2</sup> and the *infantile* and *adolescent* types of this disorder further described. The adolescent type seems to be a later, fixed stage of the deformities of the infant type but can be properly recognized as such with the aid of the history. Because of the maturity of the bones at the time it is usually recognized, the correction of adolescent bowlegs can be accomplished only by some radical surgical procedure. The infantile type of nonrachitic bowlegs, on the other hand, can be recognized early when the bones are still plastic enough to permit successful, nonsurgical treatment. A plan for this treatment is to be herewith presented as a routine which does not necessarily confine the patient to a hospital. It will be clarified by a brief review of the nature of the mechanical problem and a restatement of some observations regarding the response of growing bone to static and active forces.



## THE INFANTILE TYPE

A typical example of nonrachitic bowlegs of the infantile type can be diagnosed by x-ray. (Fig. 1.) No better description of the features of this deformity can be found than that presented by Barber<sup>2</sup> and quoted in part: "The bowing is evident as an abrupt angulation with the apex laterally just below the knee. . . . When the deformity occurs in infancy, a bulbous enlargement of the medial tibial condyle is palpable on physical examination and visible in the roentgenograms. This beaklike projection at the metaphysis has been shown to contain islands of cartilage. . . . A general medical examination usually reveals no other abnormalities. There is nothing to suggest rickets or syphilis. . . . Faulty growth of the upper tibial epiphyseal cartilage and delayed ossification of its medial half result in a wedge-shaped deformity of the epiphysis. The lower tibial epiphyseal cartilage occasionally shows similar though less pronounced changes; if this occurs, some lateral bowing just above the ankle may appear. Elsewhere the tibial shaft is perfectly straight. Secondary changes in the medial femoral condyle may augment the deformity."



Fig. 1.—Photograph of a case of moderately severe bowlegs. (Case II.) External appearance of the legs gave the clinical diagnosis which was more specifically defined as an example of "tibia vara" upon the evidence of x-ray. Bilateral but differing degrees of bowing were demonstrated with the greatest abnormality in the left leg. Arrow indicates the region of angulation and the x-ray visualizes the characteristic "spur" on the medial side of the upper tibial metaphysis where it had been palpable. The absence of evidence of rickets and the presence of an essentially straight tibial shaft can be emphasized.

An opinion regarding the nature of this localized abnormality of bone growth was expressed by Vargas in the discussion following the paper presented by Barber before the Section on Orthopedic Surgery at the annual session of the American Medical Association in 1942.<sup>2</sup> This opinion was apparently approved

by the author of the paper and the other orthopedic specialists in the group including Blount. Vargas repeated at that time that the occasional occurrence of tibia vara in a patient also having Legg-Perthes' disease, Osgood-Schlatter's disease, or the aseptic tarsal-scaphoid necrosis of Köhler led him to suspect that the unknown causes of these disorders also produced osteochondrosis deformans tibiae. This same idea has been more recently presented as a



Fig 2.—Patient, age 2 (Case V), in cast after wedging. The first application of plaster had been left undisturbed for five weeks during which time the child had been allowed all activity she could manage, including her favorite position on her back with her legs up on the side of the crib. Bone softening could actually be felt at the end of that time and the usual method of wedging was undertaken (Fig. 3). Typical of the reports of these healthy children is the following quotation from this girl's hospital record: "The patient has shown steady gain in weight . . . from her birth weight of 7 lbs. 6 oz. Feeding during infancy was an evaporated milk formula for five months followed by a cow's milk-water-karo mixture. The patient began cereal in her third month and vegetables in her fourth month. She had 3 to 10 drops of oleum percomorphum each day until about six months ago when cod liver oil was prescribed in treatment of the bowlegs which were first noted at that time."

definite fact in an authoritative work by Caffey<sup>4</sup> in which the x-ray diagnosis of all of these conditions is discussed under the single heading of "Focal aseptic necrosis" and local eschemia is mentioned as the common pathogenic mechanism. Regardless of the etiology, it can be considered an exaggeration of a physiologic deformity and, with or without treatment, expected to undergo

spontaneous progression or regression under the influence of unknown causes including the hypothetical activating effect of local trauma.

### DIFFERENTIAL DIAGNOSIS

With the features of this condition in mind, it should not be difficult to distinguish the infantile type of tibia vara from the two other conditions it most closely resembles: rickets and dyschondroplasia (Ollier's disease).

TABLE OF DIFFERENTIAL DATA

	TIBIA VARA (INFANTILE TYPE)	RICKETS	DYSCHONDROPLASIA (OLLIER'S DISEASE)
Age at onset	Second or third year	First year	Congenital
General health	Excellent	Poor: fever, weight loss, sweating, and other bone changes	Poor
Bowlegs	Bilateral but different; only objective sign	Bilateral; late in the disease	Unilateral or several bones involved besides tibia
Epiphysis	Ossification delayed in medial half	Broadened; symmetrical ossification but mottled	Irregular ossification near epiphyseal line
Epiphyseal line	Normal	Widened and vague	Broadened and vague
Metaphysis	Medial "beak" and angulation causing the bowed leg; light areas	Widened with irregular flare; calcification poor	Mottled by irregular masses of cartilage
Shaft of tibia	Straight and normal in density	Bowed with calcification poor	Bowed with irregular masses of cartilage

### TREATMENT

Since spontaneous improvement of the deformity on one or both sides has been known to occur in the milder forms of the infantile type of osteochondrosis deformans tibiae and since recurrence has also been observed when surgical correction has been undertaken before the process has become static, an attempt to treat the existing deformity by nonsurgical means is not only justified but is definitely preferable. It is assumed, of course, that the mere fact that the bowing is obvious to the child's parents gives the needed indication for treatment of some sort. As has been remarked, the immature bone in these cases of infantile nonrachitic bowlegs provides a plastic medium for the orthopedic surgeon to mold into correct alignment. Another point, previously suggested, is the fact that the abnormal bone growth process, which is not itself being treated, remains active so that the mechanically effective measures for correction must be continued until the process has become static or there will be a recurrence. In treatment it will be found expedient to use the bone softening effect of inactivity and the bone hardening effect of weight bearing to the best advantage at chosen moments. From these ideas can be constructed a plan for rational, non-surgical treatment in three stages.

1. *Immobilization Until Bone Softening Has Taken Place.*—This can be effectively accomplished in plaster casts. When applying these it is borne in mind that the tibia (near the knee) is the bone involved in the abnormal angulation and that the femur is not usually distorted. It is also evident that if the cast is

applied to make the bones soften from lack of use, any weight bearing while in the cast will defeat the plan to produce bone atrophy. As a consequence, the plaster is carried from the patient's foot to the upper thigh on each side leaving the hip joints free. The two leg casts are then rigidly joined together by a cross bar which keeps the legs in abduction to facilitate nursing care and make it impossible for the patient to stand. (Fig. 2.) The casts are made heavy enough to anchor the child to minimal activity and firm enough to stand the leverage of subsequent wedging. Added bulk is, incidentally, due to felt pads beneath the plaster in anticipation of the pressure to be exerted when wedging starts. In this restraint the bones become palpably flexible in from six to eight weeks.

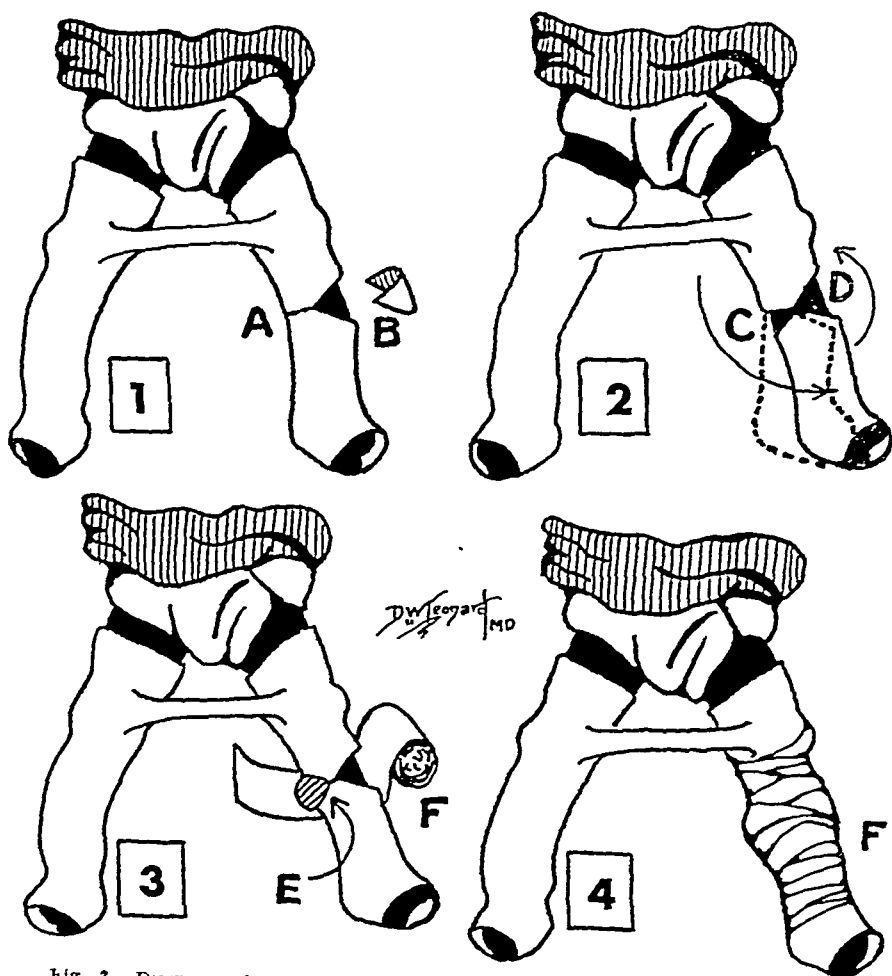


Fig. 3—Diagram of method used for the production of corrective angulation in leg casts. Cuts through the plaster are made around the cast at the level chosen (A-B) so that an elliptical piece can be removed from the outside (E). The degree of bending that the softened bone will stand must be judged by experience and may often be nearly enough to close the opening made on the outside of the cast and open a similar one on the inside (C). The latter is then filled with a mass of wadded plaster bandage (E) and the area welded together with several circular turns (F).

2. *Gradual Correction of the Bowing.*—This is undertaken by physical force when it is possible to rely on the advantage of softened bones. This is accomplished by cutting the plaster near the point of tibial angulation, forcibly correcting the abnormal angle to a degree determined by conservative judgment at the time of the manipulation and then replacing the plaster. (Fig. 3.) It is expected that this step may be repeated at two- or three-week intervals as many times as is necessary and that a new cast will be applied whenever the limit of practical wedging has been reached by the old one. Progress at any point may be checked by superimposing x-rays or by measurements on superimposed tracings. (Fig. 4.)

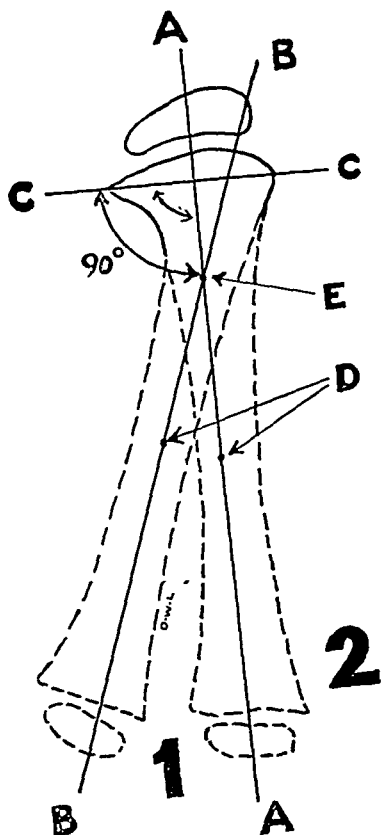


Fig. 4.—Measurement of the degree of correction made on superimposed x-ray tracings (1 and 2). The tracings are each marked with lines (C-C) which connect the medial and lateral points of the metaphysis of the tibia and are then superimposed so that these lines coincide. The parts of the bones distal to that line will then lie in a position determined by the degree of correction obtained. If a geometric evaluation is desired, it is suggested that lines (A-A, B-B) be drawn in each tracing to represent the axis of the shaft passing through its midpoint (D). These axis lines in the superimposed tracings will cross each other at the pivotal point of the corrective bending (E) and will also cross the lines C-C. Several angles can be measured but when the angle between C-C and A-A approaches a right angle the stage of theoretically perfect correction will be reached.

3. *Maintaining position.*—The final and longest stage of treatment is the maintaining of position and walking until the bones have hardened with use and the original process has become static. When satisfactory correction has been

obtained by repeated wedging and has been checked by x-ray, the casts may be discarded in favor of a pair of ambulatory braces. These braces are of the usual type and designed to exert some force in order to continue the process of correction but they are primarily intended for protection against recurrence of the

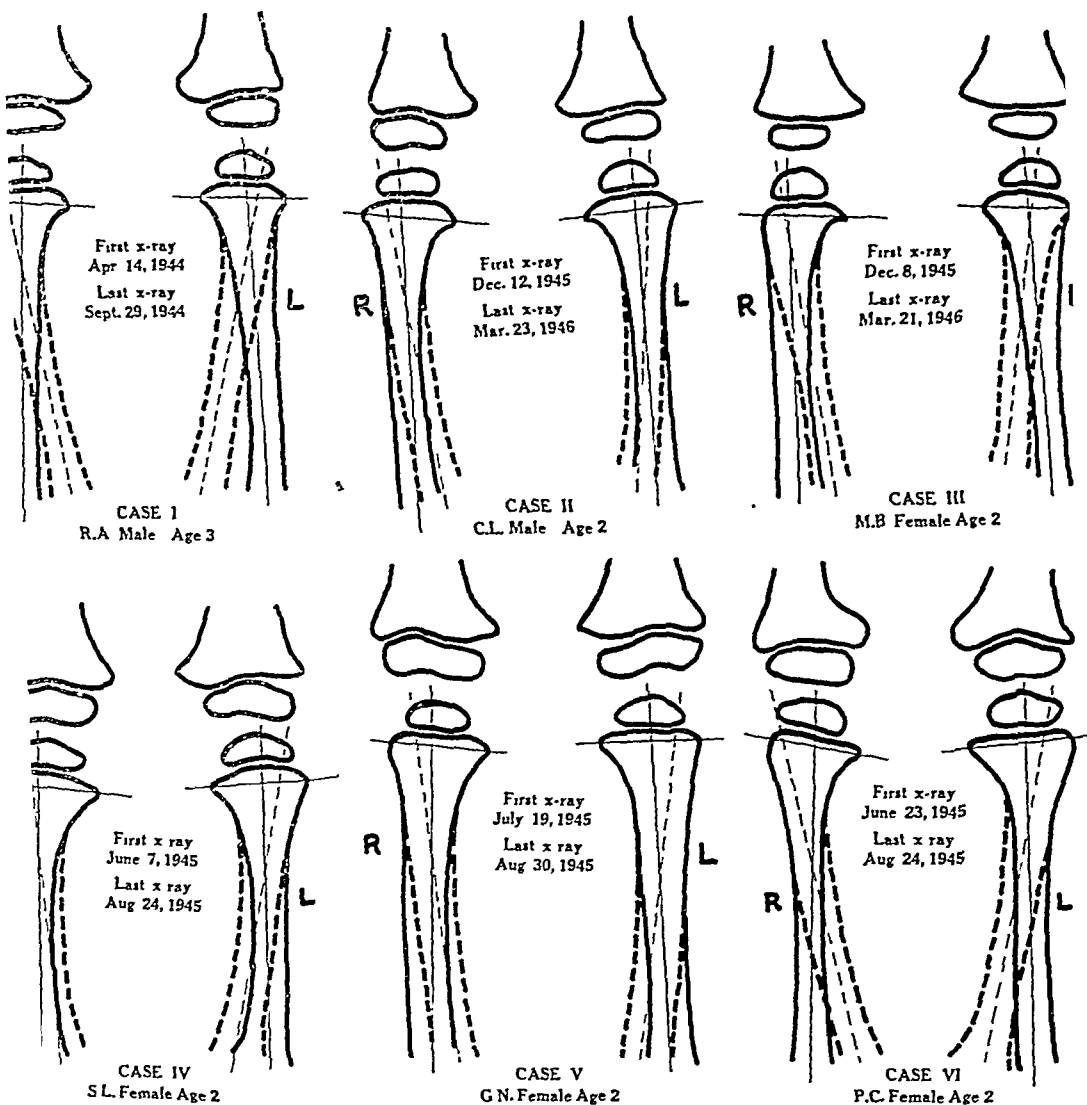


FIG 5—Photographic reductions of actual superimposed tracings of the first (broken line) and the last (solid line) x-rays taken during the treatment of six representative examples of tibia vara. Degree of improvement demonstrates that sufficient correction can be obtained by the nonsurgical method suggested.

angulation in the upper tibia. In the absence of special reasons to the contrary the patient would be expected to wear the braces continuously for six months and part of the time for another three months so that the entire duration of the treatment would be approximately one year. Resumption of weight

bearing would be relied on to hasten the hardening of the bone in the new alignment and the period of observation would be expected to make possible an immediate detection of any tendency toward recurrence.

#### REPORT OF CASES

Following this plan of treatment a number of cases of nonrachitic bowlegs of the infantile type have been treated. As a demonstration of the degree of correction it has been possible to accomplish, superimposed tracings of the first and last x-rays taken in six representative cases are presented. (Fig. 5.) Some of these patients have been hospitalized because of the provisions of the agency authorizing the work; others were cared for at home except for hospital and office calls for the actual work and the taking of x-rays.

#### SUMMARY

A definite type of nonrachitic bowlegs in childhood has been recalled with clinical and x-ray characteristics consistent enough to justify its classification as an entity under the designation osteochondrosis deformans tibiae or tibia vara. An abnormal angulation at the proximal metaphysis of the tibia is the main feature of this disorder and the cause of the gross deformity recognized as bowlegs. The shaft of the tibia is straight. The true nature of the deformity and its lack of any relationship to rickets can be demonstrated clinically and by x-ray in both the infantile and adolescent types. The first type can be corrected without surgery but the second yields only to radical methods such as osteotomy. A plan of treatment of the infantile type, based on the fact that bones in early childhood are still malleable, has been presented in three stages: (1) immobilization in plaster until the bones have softened, (2) gradual correction of the abnormal angulation by wedging of the casts, and (3) resumption of activity with the protection of braces until the abnormal growth process has become static. It has been pointed out that the plan for non-surgical treatment of nonrachitic bowlegs, as outlined, makes hospitalization optional.

It has been felt that the relatively frequent occurrence of nonrachitic bowlegs should be emphasized and that the adoption of a practical plan for conservative, nonsurgical treatment of the infantile type should be recommended.

#### REFERENCES

1. Barber, C. G.: *Am. J. Roentgenol.* 42: 498, 1939.
2. Barber, C. G.: *Am. J. Dis. Child.* 64: 831, 1942.
3. Blount, W. R.: *J. Bone & Joint Surg.* 19: 1, 1937.
4. Caffey, John: *Pediatric X-ray Diagnosis*, Chicago, 1945, The Year Book Publishers, Inc., p. 651.

# INFLUENZA VIRUS VACCINE

## LOCAL AND SYSTEMIC REACTIONS IN CHILDREN

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**I**MMUNIZATION of adults with inactive influenza virus has been reported by Hirst, Rickard, and Friedewald.\* A mild febrile response and inflammation at the site of injection were noted. However, much more severe reactions have been reported by word of mouth by numerous other people, particularly from members of the Armed Forces. With the lack of any information about dosage or reaction of children to the vaccine, 16 children between the ages of 1 and 8 years were given influenza virus vaccine, types A and B, in variable amounts.† The first four patients were given 0.25 c.c. of the vaccine subcutaneously and the temperature was recorded every 4 hours, for 36 hours or until normal (Table I).

As one patient had a mild local and systemic reaction and another a slight febrile response, six children were given 0.5 c.c. of the vaccine subcutaneously and observed as was the previous group (Table II).

In this group a mild local reaction was noted in every subject and a slight febrile reaction was noted in about one-half of the children. None of the patients appeared extremely ill nor did the local reactions seem much greater than in the previous group. Even though the severity and frequency of reactions seemed somewhat greater than in the group given 0.25 c.c., it was decided to increase the dose to the normal adult dose of 1 c.c. for six patients in a similar age group as was used previously (Table III).

The frequency of the reactions was no greater than either previous group but the severity was markedly increased. All patients had an increase in the local reaction and two of the patients were acutely ill, one having a generalized convulsion at the height of the fever (40.7° C.). Both patients were normal within 48 hours. The two older patients who were given 1 c.c. had no systemic reaction and the local reaction was about the same as in the younger patients.

The observations made in this series of patients showed that the febrile reaction in children is much more frequent than is mentioned in adults. When 1 c.c. was given, the reaction was much too severe to recommend the general use of this amount of vaccine for children. The reaction to 0.5 c.c. of the vaccine is about the same as is noted in adults when 1 c.c. of the vaccine is given. The reaction to 0.5 c.c. of the vaccine is quite mild and we think this dose is optimal and all that will be tolerated for active immunization against types A and B influenza virus. To increase the necessary immunity this dose can be repeated, perhaps, in two weeks.

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\*Hirst, C. K., Rickard, E. R., and Friedewald, W. F.: *J. Exper. Med.* 80: 265, 1944.

†Lederle. This vaccine was supplied through the courtesy of the Lederle Company, New York, N. Y.



TABLE I

SUBJECT	AGE (MO.)	REACTION			
		IMMEDIATE	12 HOURS	24 HOURS	36 HOURS
D. K.	26	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature	Normal temperature
P. W.	21	Pain; 1 cm. erythema	1.5 cm. erythema; s.c. nodule; T. 38.1° C.	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature
M. T.	14	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature	Normal temperature
E. A.	13	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; T. 38.1° C.	Normal temperature

TABLE II

SUBJECT	AGE (MO.)	REACTIONS			
		IMMEDIATE	12 HOURS	24 HOURS	36 HOURS
D. G.	14	Pain	T. 38° C.; 1 cm. s.c. nodule	1 cm. s.c. nodule	T. 38.5° C. 0.5 cm. nodule (normal 60 hr.)
B. H.	32	Pain	1.5 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	Normal temperature
D. B.	44	Pain	T. 38.6° C.; 0.5 cm. s.c. nodule	Normal temperature	Normal temperature
D. K.	33	Pain	T. 38.1° C.; 1 cm. s.c. nodule	0.5 s.c. nodule; normal temperature	Normal temperature
D. M.	36	Pain	T. 38.4° C.; 1 cm. s.c. nodule	0.5 cm. s.c. nodule; T. 38.6° C.	Normal temperature
D. S.	24	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature	Normal temperature

TABLE III

SUBJECTS	AGE	REACTIONS			
		IMMEDIATE	12 HOURS	24 HOURS	36 HOURS
J. Q.	19 mo.	Pain	1.5 cm. s.c. nodule; normal temperature	0.5 s.c. nodule; normal temperature	Normal temperature
V. P.	30 mo.	Pain	1.5 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	Normal temperature
C. F.	24 mo.	Pain	2 cm. s.c. nodule; T. 39.6° C.	1 cm. nodule; 1 cm. erythema; T. 37.8° C.	Normal temperature
R. B.	36 mo.	Pain	2 cm. s.c. nodule; 4 cm. erythema; T. 40.7° C.	1.5 cm. nodule; T. 38° C.	0.5 cm. nodule (normal 48 hours); normal temperature
M. L.	8 yr.	Pain	1.5 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	Normal temperature
P. B.	6 yr.	Pain	2 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	0.5 cm. s.c. nodule (normal 48 hr.); normal temperature

## IMMUNE RESPONSE TO EARLY ADMINISTRATION OF PERTUSSIS VACCINE

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THE prophylactic use of pertussis vaccine has become an accepted pediatric procedure. Pertussis vaccine as an immunizing agent would hardly have attained such widespread favor had clinical trial not justified its value in the prevention and amelioration of pertussis. The combined impressions of so many well-trained and competent clinical observers would seem to weight the scale heavily in favor of the routine use of this immunizing agent, occasional disparaging reports notwithstanding. It is our own experience that whooping cough, in properly vaccinated infants, has been a very infrequent and mild infection. Except for the history of intimate exposure the diagnosis in most instances would have been subject to serious question.

One of the most serious criticisms of pertussis immunization as presently practiced is the fact that we are leaving unprotected the very age group in which the more serious illness and the highest mortality rate occur. Stimson<sup>1</sup> states that in recent years, in many communities, whooping cough has caused more deaths than diphtheria, measles, or scarlet fever, and in children under 2 years of age more than these three diseases combined. Dauer<sup>2</sup> lists the whooping cough deaths by age in the United States during the years 1935 to 1939 thus:

	PER CENT
Under 3 months	40.0
6 to 11 months	24.2
1 year	21.8
2 years	7.1
3 years	3.2
4 years	1.7
5 to 9 years	2.9
10 to 14 years	0.5

As presently done it is the usual custom to administer pertussis vaccine at from 6 to 8 months of age. It has been generally believed that an adequate immune response could not be expected at a younger age in that pertussis vaccine would fail to stimulate adequate antibody response in young infants.

The purpose of this study was to observe the immune response to pertussis vaccine administered to young infants as measured by agglutinin titers at various age levels. We would clearly emphasize that we are not interested in establishing the effectiveness of any particular vaccine or type of vaccine.\*

The plan of study was: One-half cubic centimeter of a vaccine containing 40,000 million killed pertussis bacilli (phase I) was administered deep subcutaneously to 129 infants at one week of age, with a second dose of 1 c.c. at

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\*The pertussis vaccine used in this study was supplied by Cutter Laboratories, Berkeley, Calif. All agglutination tests were made at the Cutter Laboratories. This courteous cooperation and assistance are gratefully acknowledged.

one month of age, and a third dose of 1 c.c. at 2 months of age. In order to determine the advisability of a booster dose, 1 c.c. of vaccine was administered to 50 previously vaccinated infants at approximately 6 months of age and the agglutinin titer determined one week later. In a smaller group of infants the same dosage and the same interval were employed, the first dose of vaccine being administered at 2 months of age. Agglutinin titers were observed at various age periods as shown in the figure and tables.

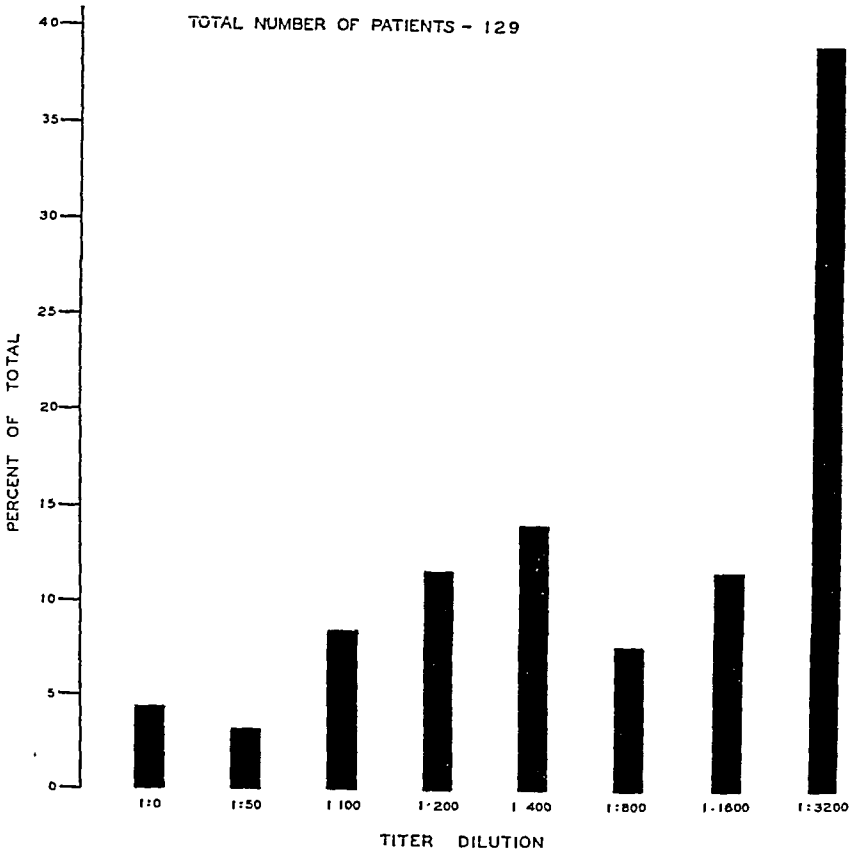


Fig. 1.

It has been shown that some passive transfer of antibodies from the mother to the newborn infant can be expected in some infants born of mothers who have had a previous attack of whooping cough. In order to establish a base line for this study the agglutinin titers of 22 unvaccinated infants one week of age were observed. Table I describes the agglutinin titers in this group of unvaccinated infants.

In 6 infants no transfer of antibodies was demonstrated. In 7 other infants the antibody content as measured by the presence of agglutinins in blood samples would seem inadequate. It would appear that inherited immunity cannot be expected with regularity in newborn infants.

TABLE I

CHART NUMBER	AGE (WK.)	AGGLUTININ TITER	CHART NUMBER	AGE (WK.)	AGGLUTININ TITER
214361	1	1:3,200	214847	1	1:200
214415	1	1:0	214873	1	1:400
214490	1	1:200	214963	1	1:0
214513	1	1:50	214900	1	1:0
214419	1	1:600	214919	1	1:0
214487	1	1:0	214968	1	1:0
214646	1	1:50	215065	1	1:100
214375	1	1:800	215046	1	1:100
214433	1	1:3,200	214187	1	1:400
214737	1	1:400	215143	1	1:200
214733	1	1:400	215176	1	1:200

TABLE II

HOSPITAL NUMBER	2 TO 3 MONTH TITER	4 MONTH TITER	6 TO 7 MONTH TITER	POST-BOOSTER TITER
208889	1:3,200	-	1:3,200	1:3,200
208598	1:400	-	1:3,200	1:3,200
208968	1:50	-	1:50	1:3,200
209036	1:3,200	-	1:3,200	1:3,200
209173	1:3,200	-	1:3,200	1:3,200
209289	1:200	-	1:800	1:3,200
210490	1:400	-	1:400	1:3,200
210515	1:3,200	-	1:400	1:3,200
210014	1:400	-	1:3,200	1:3,200
212100	-	-	1:3,200	1:3,200
208399	1:200	-	1:400	1:3,200
208373	1:200	-	1:50	1:800
208547	1:400	-	1:400	1:800
209268	1:200	-	1:400	1:400
209315	1:100	-	1:3,200	1:1,600
209193	1:400	-	1:3,200	1:800
209265	1:200	-	1:800	1:3,200
208625	-	-	1:1,600	1:800
212243	1:800	-	1:3,200	1:3,200
212289	1:100	-	1:3,200	1:3,200
212755	1:3,200	-	1:3,200	1:3,200
210757	1:0	-	1:3,200	1:3,200
214487	1:400	1:800	1:3,200	1:3,200
214646	1:100	1:800	1:0	1:50
214375	1:400	1:3,200	1:3,200	1:3,200
214433	1:3,200	1:3,200	1:3,200	1:3,200
214733	1:800	1:3,200	1:3,200	1:3,200
214847	1:3,200	1:3,200	1:3,200	1:3,200
214873	1:400	1:400	1:3,200	1:3,200
214963	1:3,200	1:0	1:800	1:1,600
214900	1:3,200	1:3,200	1:0	1:3,200
214919	1:3,200	1:3,200	1:3,200	1:3,200
215176	1:3,200	1:3,200	1:3,200	1:3,200
215174	1:3,200	1:3,200	1:3,200	1:3,200
215748	1:50	1:50	1:3,200	1:3,200
215242	1:800	1:3,200	1:100	1:1,600
215509	1:400	1:800	1:3,200	1:3,200
215665	1:400	1:800	1:1,600	1:1,600
215365	1:200	1:800	1:1,600	1:1,600
215614	1:3,200	1:3,200	1:3,200	1:3,200
215448	1:3,200	-	1:800	1:800
215476	1:800	-	1:1,600	1:1,600
216495	1:3,200	1:3,200	1:3,200	1:3,200
216596	1:3,200	1:3,200	1:3,200	1:3,200
216785	1:1,600	1:3,200	1:3,200	1:3,200
216167	1:3,200	1:3,200	1:3,200	1:3,200
217164	1:1,600	1:3,200	1:3,200	1:3,200
215667	1:400	1:3,200	1:3,200	1:3,200
216784	1:1,600	1:3,200	1:3,200	1:3,200
216783	1:1,600	1:3,200	1:3,200	1:3,200
			1:3,200	1:3,200

The early immune response to pertussis vaccine administered at this early age and measured by agglutinin response is shown in Fig. 1. Blood samples were taken from 129 infants at 9 weeks of age, one week after the administration of the third dose of vaccine. Approximately 38 per cent showed a positive agglutination test in a dilution of 1:3,200; 12 per cent in a dilution of 1:1,600; 7 per cent in a dilution of 1:800, and 13 per cent in a dilution of 1:400. An advancing rise in antibody content with increasing age is apparent in the subsequent tables.

In Table II are listed the agglutinin titers at various age periods in 50 infants in whom the study was carried to completeness. All infants received three doses of vaccine the first injection being given at one week with a booster injection at 6 to 7 months of age.

Thirty-seven of the 50 infants showed a positive agglutination test in a dilution of 1:3,200. Twelve other infants showed a positive agglutination test of 1:400 or better. In one infant the post-booster agglutinin response appeared inadequate.

In general the antibody response was well sustained throughout the period of study. These data would seem to refute the generally held belief that young infants are unable to develop an active immune response following administration of a suitable pertussis vaccine.

In Table III are listed for the purpose of comparison, the agglutinin titers at various age periods in 44 infants in which injections of pertussis vaccine were begun at 2 months of age with a booster dose of vaccine at 6 to 7 months. The immune response as measured by positive agglutination tests are quite comparable with that obtained when pertussis vaccine was administered in the neonatal period.

Thirty-seven of the 44 infants gave a positive agglutination test in a dilution of 1:3,200, one week after the administration of a booster dose of pertussis vaccine. Six other infants showed a post-booster titer of 1:400 or better. In one infant the post-booster agglutinin response appeared inadequate.

Local and systemic reactions to pertussis vaccine were negligible at this early age and were much less frequent and less severe than we were accustomed to observe when pertussis vaccine was administered to infants at the age of 7 months. The fact that a high percentage of parents cooperated to the extent that the study could be completed would seem to justify the impression that local and systemic reactions were inconsequential in nature and frequency.

#### COMMENT

A satisfactory agglutination response cannot be accepted as an absolute measure of immunity. It can be accepted, however, as a real measure of immune response. The high incidence of positive agglutination tests in high dilutions would seem to justify the expectations that the incidence of pertussis in these vaccinated infants will be less and illness modified should pertussis occur in these inoculated infants. Proof of this assumption will require mass trial over a period of months and years. It is interesting to note that while this study was in progress 2 infants shortly, after the third dose of vaccine,

TABLE III

HOSPITAL NUMBER	4 TO 5 MONTH TITER	6 MONTH TITER	POST-BOOSTER TITER
206199	1:3,200	1:1,600	1:3,200
206349	1:800	1:1,600	1:3,200
206227	1:3,200	1:3,200	1:3,200
205805	1:200	1:50	1:3,200
205633	1:1,600	1:3,200	1:3,200
206095	1:3,200	1:400	1:3,200
206112	-	1:3,200	1:3,200
206744	1:1,600	1:3,200	1:3,200
206763	-	1:1,600	1:3,200
207233	1:3,200	1:3,200	1:3,200
206364	-	1:3,200	1:3,200
C34462	1:3,200	1:3,200	1:3,200
205851	-	1:3,200	1:3,200
345960	-	1:600	1:3,200
208086	1:3,200	1:3,200	1:3,200
207942	-	1:600	1:1,600
208258	1:3,200	1:800	1:3,200
208340	1:400	1:1,600	1:3,200
208324	1:3,200	1:1,600	1:3,200
207623	1:400	1:400	1:1,600
207631	1:800	1:3,200	1:200
207720	1:3,200	1:3,200	1:3,200
207837	1:200	1:800	1:3,200
207721	1:1,600	1:1,600	1:3,200
208865	1:800	1:3,200	1:3,200
208378	1:200	1:400	1:1,600
208681	1:200	1:200	1:3,200
210407	1:1,600	1:1,600	1:1,600
209684	1:3,200	1:3,200	1:3,200
209471	1:400	-	1:3,200
209589	1:400	1:3,200	1:3,200
210004	1:800	1:3,200	1:3,200
209484	1:800	1:1,600	1:800
209485	1:400	1:1,600	1:3,200
210159	1:1,600	1:3,200	1:3,200
C36168	1:1,600	1:3,200	1:3,200
211386	1:3,200	1:3,200	1:3,200
211095	1:3,200	1:3,200	1:800
C36549	1:3,200	1:3,200	1:3,200
211232	1:400	1:3,200	1:3,200
212286	1:800	1:3,200	1:3,200
211864	1:100	1:1,600	1:3,200
212590	1:3,200	1:3,200	1:3,200
212122	1:800	1:3,200	1:3,200

were intimately exposed to pertussis in their homes. They experienced what was thought to be extremely mild pertussis when compared with the illness of other siblings in their respective families. The diagnosis would have been open to serious question had it not been for the history of intimate exposure. It would be difficult to convince the parents of these very young infants that the disease was not materially modified.

During the progress of this study the convincing report of Sako, Treuting, Witt, and Nichamin<sup>3</sup> was published. Their report of more than 16,000 infants below the age of 2 months immunized with alum-precipitated pertussis vaccine and no deaths reported in the state of Louisiana from the immunized group would seem to be indisputable evidence that pertussis can be ameliorated and often prevented by early administration of suitable pertussis vaccine. We agree thoroughly with these workers in their suggestion that the question of

when to immunize against pertussis is urgently in need of clarification. It is our present custom to advise that immunization against pertussis be started at from 6 weeks to 2 months after birth. A booster dose at 7 to 8 months may well be given as an added measure of precaution although this additional dose would not seem necessary in the majority of infants since the antibody content of the blood of vaccinated infants showed little tendency to wane over a period of 6 months, the duration of this study. A satisfactory immune response can be regularly expected when a first dose of pertussis vaccine is administered in the neonatal period. Pertussis vaccine can be safely administered at this early age period without fear of disagreeable local or systemic reactions.

#### REFERENCES

1. Stimson, P. M.: A Manual of the Common Contagious Diseases, ed. 3, Philadelphia, 1940, Lea & Febiger, ch. 8, p. 209.
2. Dauer, C. C.: Pub. Health Rep. 58: 661, 1943.
3. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S. J.: J. A. M. A. 127: 379, 1945.

## PARAPERTUSSIS PNEUMONIA

### REPORT OF TWO FATAL CASES

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THE parapertussis bacillus was first isolated by Eldering and Kendrick<sup>1</sup> from cases of apparently mild whooping cough. The organism is a small nonmotile gram-negative bacillus morphologically resembling *Hemophilus pertussis* but able to grow on non-blood-containing media. It shares minor antigenic factors with *H. pertussis* and *Brucella bronchiseptica*. A general agreement has not been reached as to its exact classification, although it is clear that it is closely related to both of these organisms. All observers agree that infections caused by this organism are considerably milder than the usual picture of pertussis.

We have recently isolated *Bacillus parapertussis*\* from two fatal cases of "whooping cough" and feel that it is important to point out that infections due to this organism are not always innocuous.

These case reports represent, to our knowledge, the first description of the pathologic findings in human parapertussis infections.

### REPORT OF CASES

CASE 1.—G.T., a 3-month-old Negro girl, was admitted to Children's Hospital of Michigan on Dec. 20, 1942, with the chief complaint of paroxysmal cough of approximately one week's duration. The illness had begun with symptoms of a cold accompanied from the start by coughing and choking. Considerable phlegm was said to be expectorated. For the last few days the baby had tended to assume a position of opisthotonos frequently associated with "rolling of the eyes." The parents noted fever and had suspected an earache because the baby was noted to pull at both ears.

The past history was noncontributory. Birth and development had been normal. The family history was interesting in that four siblings were all said to have "colds." However, the parents did not feel that any of these children had whooping cough.

Physical examination revealed a well-developed and well-nourished infant in a state of semicoma. The weight was 9 pounds, 14 ounces, the temperature 104.4° F. During the examination the entire body became stiff, the eyes rolled, and opisthotonos was observed. The attack lasted approximately two minutes. The anterior fontanel was widely patent and somewhat depressed. There was an internal strabismus of the left eye. The fundi appeared normal. The tympanic membranes were injected, the nostrils contained small amounts of mucopurulent exudate. There was slight cyanosis of the lips. The pharynx was injected. Examination of the chest revealed moist râles over both bases; the percussion note seemed normal. The liver was felt 4 cm. below the costal margin. The remainder of the findings were noncontributory.

Laboratory data.—Urine was not obtained. The white blood count was 53,000. The differential count revealed 80 per cent lymphocytes and 20 per cent polymorphonuclears. A culture of the blood taken upon admission remained sterile.

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\*The term *B. parapertussis* is used for convenience and does not imply classification of the organism in the genus *Bacillus*.



*Course.*—The child had repeated paroxysms of coughing during which she became slightly cyanotic but did not vomit. Because of the neurologic symptoms a lumbar puncture was performed shortly after admission. A "bloody tap" was obtained. The supernatant fluid contained an adequate amount of sugar as measured by a rough quantitative test and cultures remained sterile. The patient was placed in an oxygen tent and received subcutaneous injections of 5 per cent sodium sulfadiazine in water. Repeated aspiration of the upper air passages was necessary and a thick mucopurulent material was obtained. During the night the patient had repeated convulsive seizures and severe coughing spells with cyanosis. A definite "whoop" was heard. At times the convulsions were left-sided. The child expired eleven hours after admission to the hospital.

*Autopsy.*—The examination was performed four hours after death. The body was that of a well-developed and well-nourished infant. External examination revealed no significant abnormalities other than marked abdominal distention and the presence of a small umbilical hernia. The heart was distinctly large owing to dilatation of the right ventricle. The lungs were pink and crepitant except for the hilar central areas which were light purple in color and of medium consistency. A thin mucoid exudate could be expressed from the small bronchi and moderate amounts of tenacious clear mucus were present in the trachea. Aspirated stomach contents filled the lumen of the right main bronchus.

The brain weighed 565 grams (normal 516 grams) and appeared slightly tense against the dura but was not otherwise grossly abnormal. The tympanic cavities contained small amounts of clear fluid.

*Microscopic examination:* In sections of the lungs there was little involvement of the pulmonary parenchyma proper, but the alveoli here were often found distended to a moderate degree. The significant changes centered around the bronchi of large and medium caliber. The lumina of the structures were usually filled with a mixture of mucus and polymorphonuclear leucocytes. The epithelial lining was more or less densely infiltrated with leucocytes and the cilia often appeared clumped, fused, or entirely absent. There was infiltration with polymorphonuclear leucocytes in the subepithelial layer. The peribronchial connective tissue was wide and infiltrated with predominantly mononuclear cells, lymphocytes, and occasional plasma cells. The capillary plexuses around the bronchi were markedly engorged. The neighboring alveoli occasionally contained a few mononuclear cells but were usually free of exudate. Here and there small groups of alveoli were collapsed.

In the trachea the epithelial lining appeared well preserved and was only mildly infiltrated with polymorphonuclear leucocytes and lymphocytes. Attempts to demonstrate microorganisms in sections of fixed tissue by means of the modified Goodpasture stain were unsuccessful. In paraffin sections of brain tissue stained with hematoxylin-eosin, the only demonstrable change was perivascular edema in many areas and extremely rare pericapillary extravasations in the subcortical white matter.

*Bacteriologic studies:* A culture of the heart's blood remained sterile. In a smear from the lungs and from the left main bronchus, a few minute gram-negative coccobacilli were found. Pus obtained from a bronchus was cultured on 30 per cent human blood Bordet-Gengou agar. On the fifth day, tiny yellowish colonies without hemolysis appeared, composed of gram-negative pleomorphic bacilli. These organisms grew on subculture at first in two days, and later in one day as tiny colonies on 5 per cent human blood agar and chocolate proteose No. 3 agar. After three transplants they grew freely in tryptose phosphate broth. They were nonmotile, and agglutinated on a slide with anti-*H. pertussis* rabbit serum.\* The ability of the organism to grow on nonblood-containing media showed that it was not a virulent strain of *H. pertussis*, nor *Hemophilus influenzae*. However, except for an absence in our cultures of a brownish discoloration of the media, the biochemical properties were those described by Eldering and Kendrick as characteristic of *B. parapertussis*. The strain was identified by Dr. Grace Eldering, Western Division Laboratories, Michigan Department of Health, as the *parapertussis* bacillus.

\**H. pertussis* rabbit antiserum was obtained from Dr. H. C. Batson, Laboratories, Michigan Department of Health, Lansing, Mich.

CASE 2.—E. T., a 13-month-old white girl, was admitted on May 27, 1943, with the chief complaint of "whooping cough."

The child was said to have been well until two weeks before admission when she began to have a dry nonproductive cough which was not accompanied by coryza or fever. There had been whooping cough in the neighborhood and the child was taken to the family physician who made the diagnosis of whooping cough and gave three "injections." During the last week before admission the respirations became rapid, the cough was paroxysmal, and each spasm ended with expectoration of yellowish white mucuslike material. An actual "whoop" was not noted by the parents. For the last few days there was fever and three days before admission a generalized convulsion occurred. Since then the child had eaten almost nothing, the breathing had becoming increasingly rapid, and on the day of admission three other convulsions occurred. After the last convulsion the child became semicomatose and was brought to the hospital.

The past history and family history were noncontributory. The child had developed normally and had not been ill. There had been no immunization against whooping cough or other contagious diseases.

Physical examination revealed an acutely ill, cyanotic, dyspneic child in a state of coma with staring eyes and slight nystagmus. The respirations were extremely rapid and almost entirely abdominal in character. The temperature was 106° F. The lungs were hyper-resonant to percussion everywhere and fine and coarse râles were heard throughout the chest.

*Course.*—The patient was almost moribund and continued to have convulsions which were mainly right-sided and did not respond to paraldehyde administered by rectum and phenobarbital given intramuscularly. A lumbar puncture was performed yielding a spinal fluid which gave normal values for cells, sugar, and protein. Other laboratory data could not be obtained. The patient expired within eleven hours after admission.

*Autopsy.*—The examination was performed nine hours after death. Inspection of the body revealed nothing unusual except for slight flaring of the lower portion of the thorax and moderate abdominal distention. There were extensive areas of consolidation, nodular or confluent, in both lungs. The process was especially marked in the apex of the right upper lobe, the apical portion of the right lower lobe, and the left lower lobe which was involved in its entirety, but all lobes were affected. The consolidated areas on cut surface were slightly raised, grayish brown. The bronchi of all calibers contained large amounts of thick yellowish gray mucopurulent exudate, and in the consolidated areas thickening of the bronchial walls was frequently noted.

The brain weighed 80½ grams (normal 925 grams) and did not appear grossly abnormal. Considerable amounts of thick purulent yellow exudate were present in both tympanic cavities.

*Microscopic examination:* The process in the lungs was essentially similar to that described in Case 1, but much more severe and extensive and complicated by the presence of a widespread exudate of polymorphonuclear leucocytes and mononuclear cells in the alveolar lumina. The bronchial epithelium was often destroyed by ulceration and necrosis. In sections stained with modified Goodpasture stain, small slightly pleomorphic gram-negative bacteria were often demonstrable within the cytoplasm of polymorphonuclear leucocytes and mononuclear cells, but were not found within the epithelium of the bronchi. Except for congestion and evidence of cerebral edema, sections of the brain were not remarkable.

*Bacteriologic studies:* Pus from the bronchus was planted on 30 per cent human blood Bordet-Gengou medium. After six days' incubation a variety of gram-negative and gram-positive cocci had grown but there were no pertussis-like colonies. Material from the lung was inoculated on 5 per cent human blood chocolate proteose No. 3 agar. After twenty-four hours' incubation there were a few small grayish colonies composed of short poorly staining gram-negative bacilli. These organisms agglutinated on a slide with anti-*H. pertussis* rabbit serum. Pus from the right tympanic cavity grew *Micrococcus catarrhalis* and *Streptococcus hemolyticus*. The left tympanic cavity produced a growth on blood agar

in two days of tiny rounded colonies without hemolysis, composed of thin regular gram-negative bacilli. These organisms grew well on chocolate agar subcultures and also gave a positive slide agglutination with anti-*H. pertussis* serum. The strain from the ear was submitted to Dr. Eldering for confirmation and she reported: "The culture is a gram-negative coccobacillus, produces hemolysis in Bordet-Gengou medium, grows well on veal infusion agar with formation of brown pigment. The organisms were agglutinated by serum prepared against *Hemophilus pertussis* at a titer of 1:20, *Br. bronchiseptica* at a titer of 1:100, and parapertussis bacilli at a titer of 1:2,000."

#### DISCUSSION

Bradford and Slavin,<sup>2</sup> and Miller, Saito, and Silverberg<sup>3</sup> also isolated *B. parapertussis* from children with severe cough and extended Eldering and Kendrick's<sup>1</sup> observations. Miller and his co-workers, and Flosdorf, Biondi, Felton, and McGuinness<sup>4</sup> observed that specific humoral antibodies were present in the blood serum of 25 to 70 per cent of normal children.

By means of absorption experiments, Flosdorf and his co-workers were able to conclude that these agglutinins represented previous specific infections with the parapertussis bacillus and not nonspecific cross-reactions due to previous infections with, or immunization against *H. pertussis*. This evidence "suggests that only the relatively serious cases of parapertussis are diagnosed clinically and that these are similar to mild cases of whooping cough; the nature of the typical disease of parapertussis apparently is not recognized clinically in relation to the specific etiologic agent."

While no second attacks of parapertussis have been reported, the disease has been noted in children who have had pertussis and in children who have been immunized with pertussis vaccine; conversely, pertussis has been observed in children who have had parapertussis.

In Case 1 no definite history of exposure to recognized whooping cough was obtained, but upper respiratory infection associated with cough existed simultaneously in the patient's four siblings. In Case 2 the exposure to "whooping cough" was definite. The clinical picture and the pathologic findings in both cases were compatible with pertussis. The high lymphocyte count in Case 1 and the encephalopathy in both cases seemed to corroborate this diagnosis.

In view of the implications which our two cases carry in regard to the exact etiologic diagnosis of pertussis-like infections, it is essential to establish an accurate diagnosis in each of them. The diagnostic criteria for the bacteriologic identification of the parapertussis bacillus have been fulfilled in both instances.

Since the pathologic processes described are in most respects similar to those encountered in pertussis pneumonia, and since Miller isolated one of his strains of *B. parapertussis* along with phase I *H. pertussis* from a severe case of whooping cough,<sup>5</sup> one should be able to prove the absence of *H. pertussis* in order to attribute the etiology to *B. parapertussis*. The only material cultured expressly for *H. pertussis* was the bronchial secretion. These cultures, however, were examined carefully for *H. pertussis* which was not found. It would be

more convincing if the material from the lungs had been so cultured. In Case 1 the lung culture was sterile. In Case 2 the parapertussis bacillus was isolated from the lung in pure culture, and from the ear, an unlikely occurrence if the organisms were merely secondary invaders. Therefore, it is reasonable to conclude that *B. parapertussis* was responsible for the fatal disease in each case.

The frequency with which parapertussis can cause serious and even fatal forms of "whooping cough" remains to be determined. Judging from our experience until 1942, few attempts are made in routine pathologic work to establish on an accurate bacteriologic basis the etiology of cases of whooping cough at autopsy. The pathologist is usually satisfied to render a diagnosis of interstitial pneumonia compatible with whooping cough, and means for the exact identification of pertussis-like organisms are not always available. It is quite possible that the two cases reported were rare exceptions to the rule that parapertussis infections are not fatal, but the occurrence of these two cases within less than one year would suggest the opposite. Only painstaking observations made jointly by the clinician, pathologist, and bacteriologist can settle this point. Since parapertussis bacillus is not included in the whooping cough vaccines now recommended, and since there appears to be little cross-immunity between infections with *H. pertussis* and *B. parapertussis*, the problem is obviously of more than theoretic importance.

#### SUMMARY

1. Two cases of fatal pertussis-like infections in infants are reported with autopsy studies.
2. The etiologic agent was demonstrated to be *B. parapertussis*, instead of *H. pertussis*, upon bacteriologic, rather than pathologic, evidence.
3. The diagnosis of pertussis at autopsy should not be made without bacteriologic confirmation.
4. Parapertussis may be a more serious disease than formerly thought.

The authors wish to express their indebtedness to Dr. Grace Eldering and Dr. Pearl Kendrick for confirming the organisms isolated, and for their helpful suggestions.

#### REFERENCES

1. Eldering, G., and Kendrick, P.: *J. Bact.* 33: 71, 1937.
2. Bradford, W. L., and Slavin, B.: *Am. J. Pub. Health* 27: 1277, 1937.
3. Miller, J. J., Jr., Saito, T. M., and Silverberg, R. J.: *J. PEDIAT.* 19: 229, 1941.
4. Florsdorf, E. W., Biondi, A., Felton, H., and McGuinness, A. C.: *J. PEDIAT.* 21: 625, 1942.
5. Eldering, G., and Kendrick, P.: *J. Bact.* 35: 561, 1938.

MISTREATMENT OF CONGENITAL HEMOLYTIC DISEASE  
(ERYTHROBLASTOSIS FETALIS)  
BY TRANSFUSIONS OF Rh-POSITIVE BLOOD  
AND MATERNAL SERUM

A CASE REPORT

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SO MUCH evidence<sup>1-8</sup> has now accumulated demonstrating the superiority of Rh-negative blood over Rh-positive blood in the treatment of congenital hemolytic disease caused by Rh sensitization, that it seems hardly necessary to reiterate this point. However, a recent letter to the editor of the *Journal of the American Medical Association*<sup>9</sup> and an article recently published in the *JOURNAL OF PEDIATRICS*<sup>10</sup> show that misconceptions concerning the pathogenesis and treatment of this disease still exist. The latter article appeared even though the fallacies in the former had been pointed out by Diamond and Denton<sup>11</sup> and by Liber.<sup>12</sup> It seems to us that only misinformed or misguided physicians would nowadays treat such cases with Rh-positive blood; unfortunately, such physicians would not be qualified to evaluate critically the results of their treatment. An exception to this statement is the report by Brandes and Cushman.<sup>13</sup> These authors described an infant with severe hemolytic disease who failed to improve despite transfusions of a total of 220 c.c. of Rh-positive blood (an amount almost equal to the total blood volume), but who then rapidly and completely recovered after two transfusions of a total of only 160 c.c. of Rh-negative blood. In the carefully controlled study by Mollison,<sup>14</sup> in which erythroblastotic infants were transfused with mixtures of Rh-positive and Rh-negative blood, the Rh-negative blood survived in the infant circulations for periods of two to three months while the Rh-positive blood was eliminated within a period of several hours or days.

Since, in the present state of our knowledge of this subject, we do not feel that deliberate transfusions of Rh-positive blood to erythroblastotic infants are justifiable, we were morally prevented from performing further experiments along these lines. It occurred to us that a search of hospital records should reveal suitable examples of mistreated cases of congenital hemolytic disease in the days before the Rh factor was known. Our expectations have been fully satisfied and several such cases were found without difficulty. The purpose of this paper is to describe one of these cases, which may help convince even the most obstinate skeptic.

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Read before the Society for the Study of the Blood, May 15, 1946.

## CASE REPORT

L. H., the mother of our patient, gave the following obstetric history: The first pregnancy ended at term, Oct. 1, 1935, with the delivery of a normal female infant weighing 8 pounds, 3 ounces. This girl never showed any signs of anemia or jaundice during the neonatal period and at 10½ years of age was in good health.

The second pregnancy also ended at term, in September, 1939, when a female child was born. This infant, our patient, developed jaundice and anemia shortly after birth, and died at the age of 5 weeks as a result of improper transfusion therapy.

The third pregnancy terminated on July 15, 1942, with an 8-month stillborn female fetus which had been dead in utero for three weeks before delivery.

The results of grouping and Rh tests of the mother, father, and the living sibling are shown in Table I.

TABLE I

BLOOD OF	GROUP	MN TYPE*	Rh-Hr TYPE
Patient's father	O	MN	Rh,Rh <sub>1</sub>
Patient's mother	O	N	rh
Patient's sister	O	N	Rh,rh

\*The MN type is hardly ever of clinical importance and is included only for the sake of completeness.

It will be seen that in accordance with the expectations from the obstetric history, the patient's mother is Rh negative while the father is almost surely homozygous for the Rh factor because he belongs to subtype Rh,Rh<sub>1</sub>, i.e., he is Hr negative.\* Presumably, the mother became sensitized as a result of her first pregnancy because it will be seen that the living child, although herself unaffected, is Rh positive (subtype Rh,rh). Since the second child, our patient, also had to be Rh positive for genetic reasons, she developed congenital hemolytic disease. Moreover, at the time of delivery, some of this infant's blood gained access to her mother's circulation and increased the degree of the mother's sensitization. This accounts for the stillbirth at the third delivery. This history is typical of so-called univalent antibody disease, in accordance with Wiener's theory.<sup>16</sup> Univalent antibodies (glutinins or blockers), being comprised of smaller molecules than bivalent or multivalent antibodies (agglutinins), can traverse the placenta into the fetal circulation during pregnancy, thus giving rise to anemia or, in more severe cases, to stillbirths with hydrops.<sup>17</sup>

Our tests for Rh sensitization were performed in April, 1946, almost four years after the last delivery, so that ample time had elapsed for the antibody titer to fall. In tests carried out by the agglutination technique, Rh antibodies of only one unit titer were demonstrable, while by the conglutination technique,<sup>18</sup> the antibody titer was two units. The fact that the titer was higher in plasma media than in saline is evidence that the patient's serum contained univalent as well as bivalent antibodies, in accordance with the requirements of the theory.

The clinical history of the patient in whom we are primarily interested is: The infant was born on Sept. 2, 1939, at 11:20 A.M. after a six-hour labor, terminating with a spontaneous delivery. Her condition at birth was good, the weight being 7 pounds, 8 ounces, and the length 49 cm. The vernix was yellow. There was faint cyanosis about the mouth and slight dyspnea, but the infant was normally active. The liver was enlarged to three finger-breadths below the costal margin but the spleen was not palpable at first.

The following morning, the baby's skin was noted to be slightly icteric. A blood count showed 70 per cent hemoglobin concentration with 3,600,000 red cells per cubic millimeter, and the blood smear showed 50 nucleated red cells for each 100 white cells. The infant was treated with repeated blood transfusions, the father and the father's brother† acting as donors for almost all of them. The first transfusion was given in the afternoon of September 3, 80 c.c. of the father's blood being injected. The following day the hemo-

\*For the latest improved nomenclature of the Rh-Hr types, see Wiener and associates.<sup>22</sup>  
†Recent tests showed this individual to belong to type ON Rh<sub>1</sub>rh.

globin was 93 per cent but, by September 5, the hemoglobin concentration had dropped back to 77 per cent, the jaundice was more pronounced, and the infant was somewhat more listless. Despite this, the number of nucleated red cells had dropped to one per 100 white cells. Thereafter the blood smears were practically free of nucleated red cells.

The patient was given two small subcutaneous injections of whole citrated blood and serum from the family donors as well as intravenous injections of 75 to 85 c.c. of citrated blood. Despite this, the hemoglobin concentration ranged between 60 and 75 per cent. The jaundice became deeper, the liver and spleen remained enlarged, and the abdomen was distended. In addition, the infant was listless, nursed poorly, and slept most of the time.

After the mother was discharged from the hospital on the ninth day, the infant was transferred to the pediatric service where the same treatment was continued; namely, transfusions of whole citrated blood from the father and uncle.

TABLE II

DATE	HEMO- GLOBIN (PER CENT)	ERYTHRO- CYTES (MILLIONS PER CU. MM.)	NUCLEATED R.B.C. PER 100 W.B.C.	INTRAVE- NOUS BLOOD TRANS- FUSIONS	OTHER INJECTIONS
Sept. 2, 1939			50		
3	70	3.60	36	80 c.c.	
4	93	---	22		
5	77	3.80	1		40 c.c. blood subcutaneously
6	94	4.80		40 c.c.	
7	74	3.60			40 c.c. blood subcutaneously
8	67	2.26			20 c.c. serum (uncle's, subcutaneously)
9	60	2.25		75 c.c.	
10	66	1.83		85 c.c.	
11	75	3.27			
12	74	2.94	1		
13	71	3.01			
14	74	3.08			
15	74	3.50			
16	71	2.97			
18	67	2.31		75 c.c.	
19	--	---		90 c.c.	
20	81	3.98			
23	74	3.76			
26	67	3.12			
27	--	---		50 c.c.	
28	--	---		45 c.c.	
29	74	3.48	Reticulocytes 40/1,000		
Oct. 1, 1939	74	3.61			
3	56	2.14			
4	50				0.5 c.c. liver extract
5	--	---			20.0 c.c. maternal serum
6	28	1.28	Reticulocytes 60/1,000	75 c.c.	5.0 c.c. maternal serum
7	Exitus			Total: 615 c.c. blood	

A summary of the blood counts and transfusions is given in Table II. It will be seen that while the usual case of congenital hemolytic disease nowadays rarely requires more than 250 c.c. of blood to effectuate a permanent cure when Rh-negative donors are used, this child, by October 5, at the age of 33 days, had received a total of 615 c.c. of blood intravenously without noticeable improvement. The jaundice was still present; the liver and spleen were hard, the former four fingerbreadths and the latter two fingerbreadths

below the costal margin. Despite parenteral liver and iron therapy as well as blood transfusions, the blood count continued to drop until, on October 5, it was only 50 per cent.

At this time a report was found in the medical literature claiming favorable results from intramuscular injections of maternal serum in cases of erythroblastosis fetalis. Consequently, 20 c.c. of maternal serum were injected into the infant, and the subsequent course demonstrated the harmful results of such premature publications of new therapeutic procedures.

The following morning the blood count was found to have dropped precipitously, the hemoglobin concentration being only 28 per cent and the red cell count 1,250,000. The infant, who for a while had been quite active and playful, became listless once more, and did not take her feedings well. The connection between this reaction and the serum injection not being appreciated at the time, another 5 c.c. of maternal serum were injected. Because of the infant's desperate condition, 75 c.c. of citrated blood from a new donor were also transfused. Twenty minutes after the transfusion was completed, the infant's respirations became grunting and rapid, and her extremities cold and cyanotic. She was treated for peripheral collapse. During the night she voided a small quantity (5 c.c.) of dark amber urine which gave a positive reaction for bile and blood although no red cells were seen microscopically. The temperature rose to 103.6° F. The following morning at 7:30 A.M., the infant suddenly vomited about 3 ounces of black material which gave a 4 plus benzidine reaction. The respirations became gasping and the infant died ten minutes later.

The following were the pertinent post-mortem findings as reported by Dr. David M. Grayzel: gross examination revealed marked yellow-green discoloration of the skin and conjunctivae. There was no edema of the skin, and no free fluid in any of the body cavities. In the chest subpleural and subpericardial petechiae were noted. The stomach contained yellow-green and dark brown material, and its mucous membrane was discolored yellow-green. All the organs showed yellow-green discoloration on section. There was marked hepatomegaly (liver weighed 342 grams; average normal for age only 120 grams) and splenomegaly (spleen weighed 60 grams; average normal only 16 grams). The kidneys were normal in size, and the cortex and medulla were well demarcated. There was marked hyperplasia of the bone marrow. The brain showed no kernicterus. Microscopic examination of the liver showed inspissated casts of bile pigment in the canaliculi, and numerous islands of hematopoiesis. No agglutination thrombi were found in the brain. The kidneys showed numerous hemoglobin casts and occasional red cell casts in the collecting tubules.

There is no doubt that the patient's prolonged illness and eventual death were due to the improper treatment, which in turn was caused by lack of understanding of the pathogenesis of the disease at the time when this infant was born. The use of Rh-positive blood was ineffectual because the patient's body contained an excess of univalent Rh antibody, sufficient not only to destroy all of her own blood but also the additional Rh-positive blood introduced by transfusion. One of us (A. S. W.) has shown<sup>17, 18</sup> that such patients respond rapidly to transfusions of Rh-negative blood even though the presence of univalent Rh antibodies can be demonstrated in their serum for periods of a month or longer. These antibodies apparently do no harm as long as no "fuel is added to the fire," and they are gradually eliminated from the body. As long as they are present, they do destroy any new Rh-positive red cells produced by the infant as soon as they enter the circulation. This process is so gradual, however, that the body readily eliminates the products of this blood destruction without harm. The final disappearance of the antibodies and resulting cure is heralded by the appearance of reticulocytes in the blood smear, which usually occurs about the sixth week. Naturally, when the in-



fant's body contains only small amounts of Rh antibodies, the disease is self-limited and recovery follows quickly whether Rh-positive or Rh-negative blood is transfused.

The culminating insult in this case, of course, was the injection of maternal serum, particularly at a time when the maternal antibody titer was near its peak.\* This brought about a pronounced exacerbation of the hemolysis and the infant's death, just at a time when recovery was to be expected.

#### COMMENT

The argument for the use of Rh-positive blood when treating erythroblastotic infants, in order to absorb the excess antibodies and thus bring about a cure more rapidly, is fallacious. The body can adapt itself to many things provided sufficient time is allowed. For example, an acute hemorrhage of only one-third of the total blood volume may cause death, while slow bleeding, depleting as much as 80 per cent of the red cells, is not incompatible with life.

The other argument that Rh-negative blood donors are not always available is also untrue, because the mother, who is the ideal donor for all cases of erythroblastosis, including those due to A-B sensitization,† is usually at hand. The only precaution required is that the mother's red cells be washed with saline solution in order to remove the plasma containing the harmful antibody. Since infants require relatively small quantities of blood, the procedure of washing the red cells can be carried out in culture tubes in an ordinary laboratory centrifuge. Two washings are sufficient and since all grouping and matching tests may be omitted when maternal red cells are transfused,<sup>6</sup> this takes even less time than the regular procedure, especially when, as is sometimes necessary, one must wait for long periods for professional donors to make their appearance.

Incidentally, we prefer to use fresh blood rather than bank blood for treating erythroblastotic infants, as overage blood will break down faster in the circulation. Thus, fresh blood is more efficient than stored blood of uncertain age or of an uncertain state of preservation. The use of maternal blood is also more convenient because, following the second washing, it is possible to remove the entire supernatant fluid leaving the packed cells which can then be transfused by adding only a minimal amount of saline to reduce the viscosity. In this way a double dose of red cells can be given in the same small volume at a single transfusion, and rarely are more than two or three such transfusions required to effectuate a permanent cure.

#### SUMMARY

A case is presented which demonstrates the ineffectiveness of Rh-positive blood as compared with Rh-negative blood, and the danger of the use of maternal serum when treating infants with congenital hemolytic disease.

\*The antibody titer usually rises during the fortnight following the delivery.<sup>19</sup>

†In cases due to A-B sensitization, it is our practice to add 10 c.c. of Witebsky's solution of group substances to the washed maternal red cells; we also inject 10 c.c. of the group substance into the umbilical cord vein at birth.

## REFERENCES

1. Wiener, A. S., and Wexler, I. B.: *Am. J. Clin. Path.* 13: 393, 1943.
2. Wiener, A. S.: *Am. J. Clin. Path.* 14: 52, 1943.
3. Wiener, A. S., Wexler, I. B., and Gamrin, E. L.: *Am. J. Dis. Child.* 68: 317, 1944.
4. Wiener, A. S.: *Tr. & Stud. Coll. Physicians, Philadelphia* 13: 105, 1945.
5. Wiener, A. S.: *J. Lab. & Clin. Med.* 30: 957, 1945.
6. Wiener, A. S.: *Am. J. Dis. Child.* 71: 25, 1946.
7. Gimson, J.: *Brit. M. J.* 2: 393, 1943.
8. Leonard, M. F.: *J. PEDIAT.* 27: 249, 1945.
9. Darrow, R.: *J. A. M. A.* 127: 1146, 1945.
10. Danis, P. G., Eto, J. K., and Sennott, J. S.: *J. PEDIAT.* 28: 457, 1946.
11. Diamond, L. K., and Denton, R. L.: *J. A. M. A.* 128: 686, 1945.
12. Liber, A. F.: *J. A. M. A.* 128: 686, 1945.
13. Brandes, E. B., and Cushman, H. R.: *J. PEDIAT.* 25: 239, 1944.
14. Mollison, P. L.: *Arch. Dis. Childhood* 18: 161, 1943.
15. Wiener, A. S., Sonn, E. B., and Polivka, H. R.: *Proc. Soc. Exp. Biol. & Med.* In press.
16. Wiener, A. S.: *New York State J. Med.* 46: 912, 1946.
17. Wiener, A. S.: *Am. J. Dis. Child.* 71: 14, 1946.
18. Wiener, A. S.: *J. Lab. & Clin. Med.* 30: 662, 1945.
19. Hurst, J. G., Taylor, H. C., and Wiener, A. S.: *Blood.* In press.
20. Sanford, H. N., and Gerstley, J. R.: *J. PEDIAT.* 28: 574, 1946.
21. Henry, N. R.: *M. J. Australia* 1: 395, 1946.

## ADDENDUM

While this article was in press, a report by Sanford and Gerstley<sup>20</sup> appeared, which illustrates again the importance of using washed maternal cells for transfusing erythroblastotic infants, in cases where the exact pathogenesis is obscure. The patient had to be given the tremendous total of 2,200 c.c. of blood before the hemolytic process was arrested, whereas one-tenth of that amount of blood usually suffices when washed maternal cells are used. The grouping results (mother subgroup A<sub>1</sub>B) suggest that the abnormal antibody in the maternal serum must have been an anti-O agglutinin, as in the case recently reported by Henry.<sup>21</sup> If this conclusion is correct, then transfusions of blood of subgroup A<sub>1</sub>B would have been equally satisfactory, in case there was any objection to the use of maternal blood.

# ERYTHROBLASTIC ANEMIA OF COOLEY

## OBSERVATIONS ON THE EFFECT OF SPLENECTOMY PERFORMED ON IDENTICAL TWINS

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COOLEY and Lee<sup>1</sup> in 1925, clearly defined a clinical syndrome which they later designated as "erythroblastic anemia."<sup>2</sup> In so doing they differentiated erythroblastic anemia from a large group of unrelated anemias and splenomegalias that occur in children.

The distinctive features of the disease in its classical form are so well known that they merit only brief mention. The condition, usually attributed to a developmental defect of the hemopoietic system, is characterized by a severe and progressing anemia with large numbers of erythroblasts in the peripheral blood; a constant racial and familial incidence; enlargement of the spleen and liver; x-ray and histologic changes in the bones; pigment abnormalities; and mongoloid facies.

Despite innumerable investigations in which various substances and procedures have been tried in an attempt to find a remedy for this condition, none has proved successful. The majority of therapeutic measures tried produced no effect; transfusions temporarily alleviate the symptoms; certain other measures have been too incompletely studied to permit any definite conclusions regarding their effectiveness. Into this latter group is the operative removal of the spleen. The reports concerning the effect of splenectomy are contradictory. A few writers, Baty, Blackfan, and Diamond<sup>3</sup> and Custer<sup>4</sup> describe the operation as failing to modify the symptoms, while others, Hitzrot,<sup>5</sup> Cooley and Lee,<sup>6</sup> and Whipple and his co-workers,<sup>7</sup> describe the beneficial effects.

In view of this inconclusive evidence, this report recording the striking good effects of splenectomy in identical twins seems justified. The twins were suffering from a classical form of the disease, which in each child appeared to be of equal severity. Soon after admission the spleen was removed from one child. Both twins were then followed for fifteen months. The effects of the splenectomy were so spectacularly successful that fifteen months later a splenectomy was performed on the other. The results of the observations are described:

The identical twins, N. and A. P., were male children of Greek parentage, born in this country May 10, 1938. The birth weights were 5 pounds and 5 pounds, 1 ounce, respectively. Both were considered well until the age of 10 months, at which time a severe anemia was first recognized. Both were studied and treated in the hematological clinic at the New York Hospital, and at the time of admission to the Harriet Lane Home (Oct. 10, 1943) presented the following picture:

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N. P. (A-32420), aged 5 years, 5 months, was pale but active. He had a typical mongoloid facies. The skin and sclerae were a muddy yellow color. The eyes were slanting. The heart was enlarged and a loud blowing systolic murmur was heard over the precordium. The murmur was thought to be hemic in origin. The abdomen was protuberant and the liver edge was palpable two fingerbreadths below the costal margin. The edge of the spleen extended to the crest of the ilium and filled the whole left side of the abdomen. X-ray examination of the bones revealed the characteristic changes of Cooley's anemia.

A. P. (A-32419) was pale and not very active. He likewise had a typical mongoloid facies with muddy yellow skin and slanting eyes. Both the skin and sclerae were moderately icteric. The heart, like that of his brother, was slightly enlarged and a loud hemic murmur, systolic in time, was heard over the precordium. The striated muscle tone was poor and the abdomen was protuberant. The liver extended two fingerbreadths below the costal margin and the tip of the spleen to and into the iliac fossa. X-ray examination revealed changes in the skeleton similar to those of the brother and were characteristic of Cooley's anemia.

	N. P.	A. P.
STS	Neg.	Neg.
RBC	1,690,000	1,760,000
Hbg (Sakli)	4 grams	4 grams
WBC	12,500	14,800
Nucleated RBC per 100 WBC	10	10
Reticulocytes (per cent)	4	4
Platelets	145,000	205,000
Van den Bergh	1.6	I.I.-13
Fragility Test		
Hemolysis began	0.66	0.66 (control 0.42)
Incomplete at	0.21	0.21 (control incomplete at 0.21)

Soon after the twins were hospitalized, blood studies were performed on the parents, who were Greek émigrés. That of the father was found to be normal, but the mother's blood showed a marked anisocytosis and poikilocytosis. Although it did not contain erythroblasts and little evidence of anemia was found, the mother was considered to exhibit a trait of Cooley's anemia and possibly to harbor a defective gene capable of producing the disease in her offspring.

On admission to the hospital, except for a height difference of 1 to 2 cm. and a weight difference of 0.6 kg. in favor of A. P., the twins presented almost identical x-ray, clinical, and laboratory findings. Initial treatment consisted of bed rest and repeated transfusions of whole blood. This form of therapy was continued over a five-month period during which time the clinical picture and blood studies showed little change. In March, 1943, five months after admission, the spleen was removed from A. P. Until time of operation both boys had gained 0.5 kg. and had required essentially the same amount of blood by transfusion to maintain a hemoglobin content above 5 Gm. per 100 c.c. of blood.

#### EFFECTS OF SPLENECTOMY

During the 15 months following the operation on A. P., he grew taller and gained more weight than his twin. Further, the splenectomized twin needed only one-third to one-fifth the amount of blood required by his unoperated brother.

In May, 1945, fourteen months after the splenectomy on A. P., it became apparent that N. P. was gradually requiring larger and larger amounts of blood to maintain a level of 5 Gm. hemoglobin per 100 c.c. of blood. Although no quantitative determination of the urobilin excretion in the urine and feces was made at this time, determinations of urinary iron excretion and Van den



Fig. 1.—Photograph of x-ray films of long bones, hands, feet, and skull of N. P.

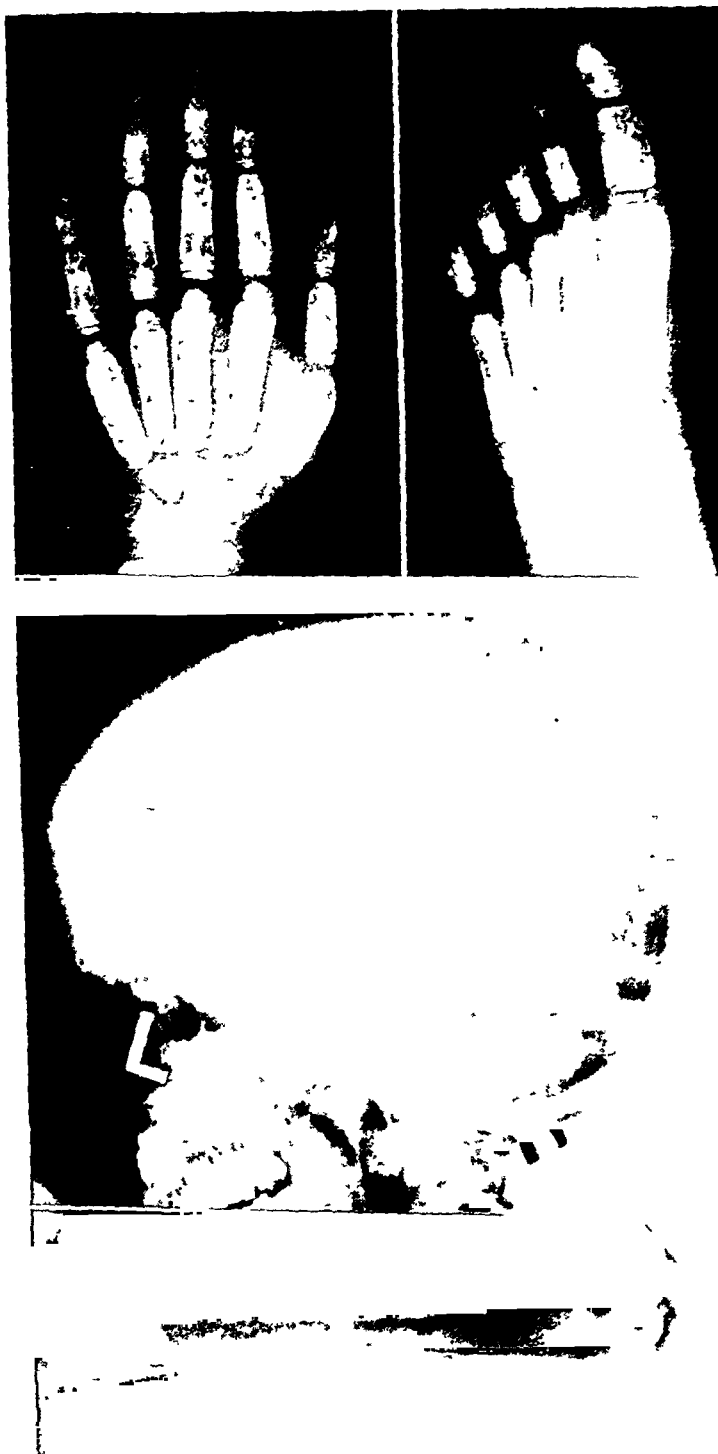


Fig 2.—Photograph of x-ray films of long bones, hands, feet, and skull of A. P.

Bergh tests showed no evidence of hemolysis. For these reasons and because N. P.'s spleen was so enormous, it was removed.

The effect of splenectomy in the two children is shown in Charts I, II, III, and IV. The changes that occurred in both were clear-cut and essentially the same. Neither child was cured, but in each the symptoms were greatly alleviated. The most striking result following the removal of the spleen was

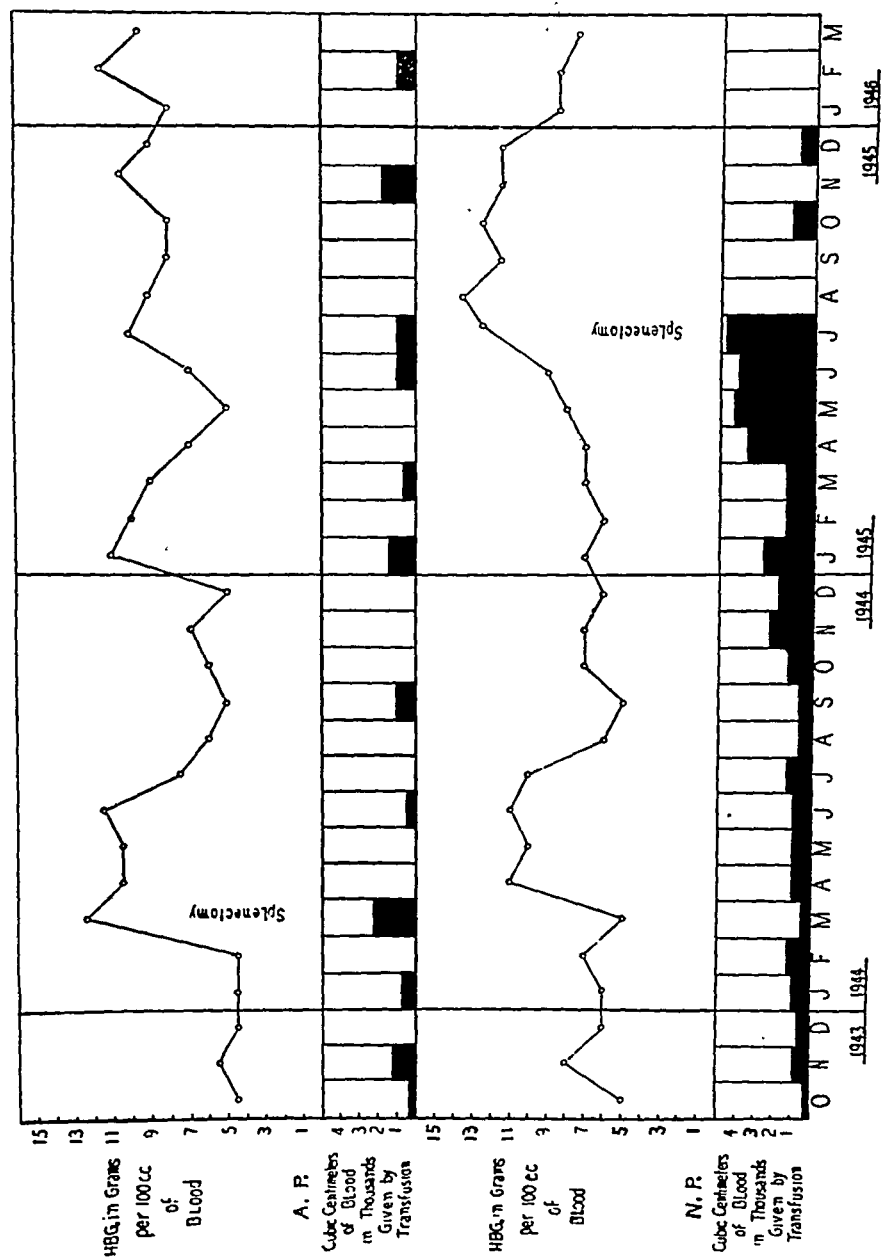


Chart I—Chart shows cubic centimeters of blood received by A. P. and N. P. each month from October, 1943, to March, 1946. The hemoglobin levels represent the highest level in grams per 100 c.c. of blood for each month.

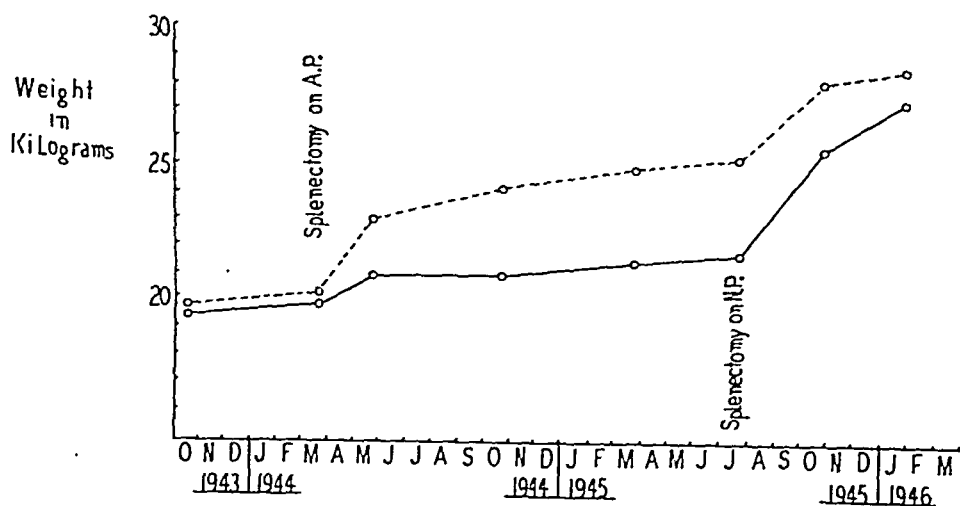


Chart II.—Chart shows weight in kilograms of the twins from October, 1943, to January, 1946. Broken line, A. P.; solid line, N. P.

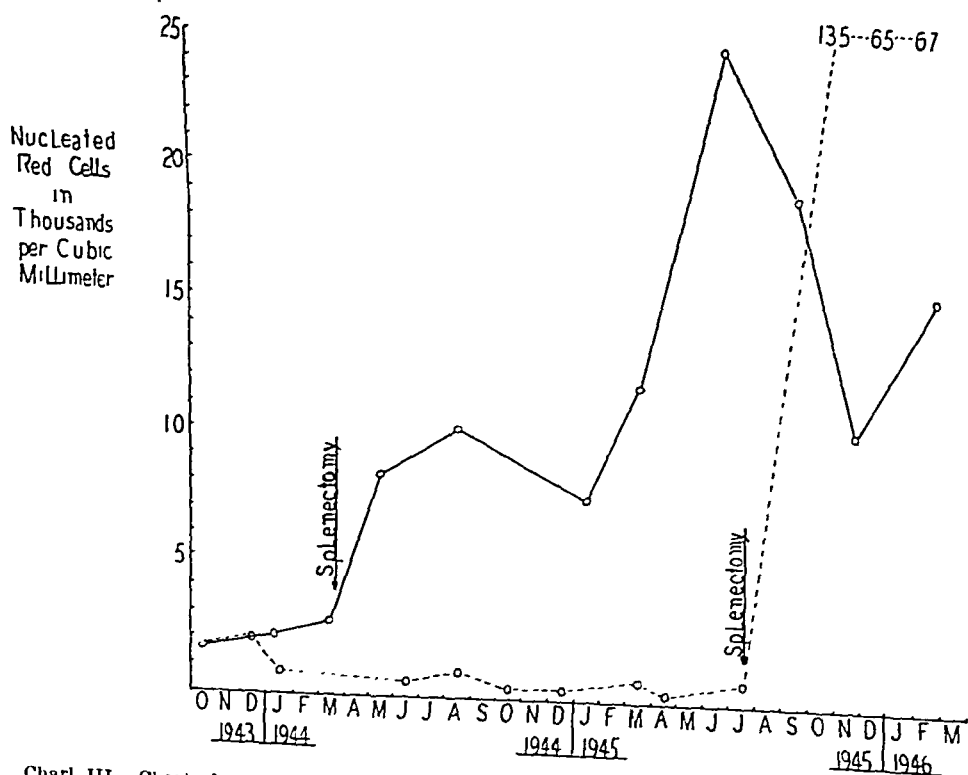


Chart III.—Chart shows the effect of splenectomy on the number of nucleated red cells per cubic millimeter. Solid line, A. P.; broken line, N. P.



that transfusions needed to maintain a critical level of 5 Gm. hemoglobin per 100 c.c. were required at two- to four-month intervals in contrast to the transfusions required weekly before operation. Also each twin made substantial weight gains following the operation and in February, 1946, N. P. had improved to such an extent that he had become comparable to his brother in signs and symptoms.

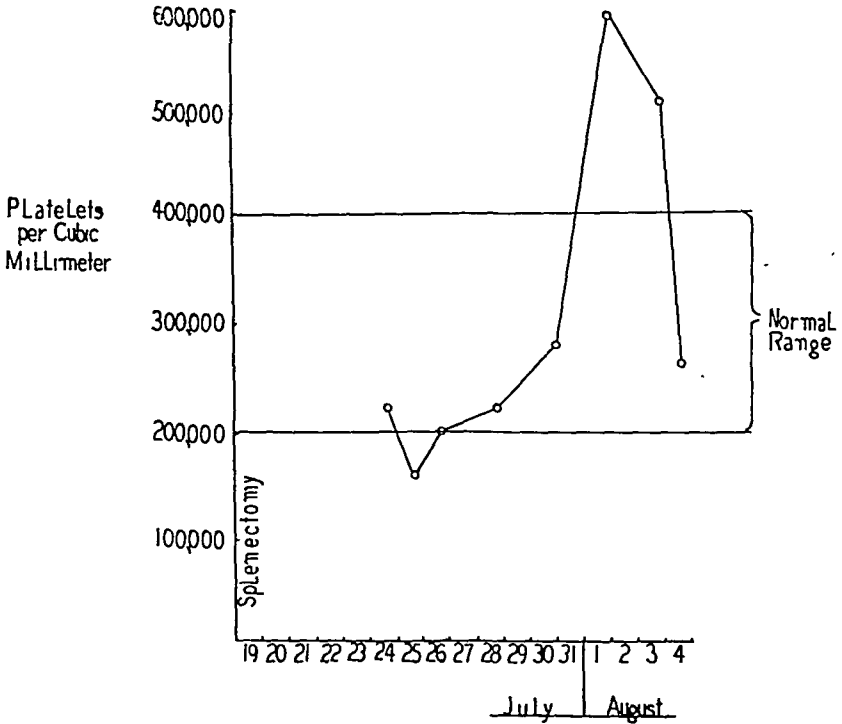


Chart IV.—Chart shows effect of splenectomy in N. P. upon the number of platelets.

#### EFFECT OF SPLENECTOMY ON THE BLOOD

The remarkable changes which occur in the peripheral blood following the removal of the spleen have been adequately described by numerous observers, Baty, Blackfan, and Diamond,<sup>3</sup> Whipple, Reeves, and Cobb,<sup>7</sup> Bradford and Dye,<sup>8</sup> and Cooley, Witwer, and Lee.<sup>2</sup> Similar changes were observed in the twins here reported. The red cell count and hemoglobin content remained essentially unchanged. There was an increase in the number of leucocytes, immature cells, and platelets. Except for the striking and persistent change in the number of nucleated red cells, the changes that occurred following splenectomy in these patients with Cooley's anemia appear to be not unlike those that occur following splenectomy in the normal individual. The nucleated red cells, however, increased in number immediately after the spleen was removed in both children and have persisted since operation. In February, 1946, 10,000 to 15,000 nucleated red cells per cubic millimeter were found in the blood of A. P. and 60,000 nucleated red cells were found in the blood of N. P.

The changes in the number of blood platelets followed a pattern described by Connors.<sup>9</sup> The platelets began to increase seven days after splenectomy and reached a maximum thirteen days after operation and then gradually returned to normal (Chart IV).

#### DISCUSSION

The effect of splenectomy in these two children has been striking and beneficial. Whether the improvement is only temporary remains to be determined. The changes, however, have persisted for two years in A. P. and a similar effect has been observed in N. P. for nine months, to the time of this report (March, 1946). Besides causing the improvements noted, removal of the large splenic mass increased the comfort of the children.

The explanation of why splenectomy modified the symptoms in these children is not clear. We know that to maintain a given blood level, the rate of blood destruction must equal the rate of blood formation. In patients with Cooley's anemia one or both of these functions fails and to sustain life repeated infusions of blood are necessary. The manner in which the spleen affects either of these functions is obscure, but it was obvious that following splenectomy much less transfused blood became necessary to maintain a level of 5 Gm. (critical level) hemoglobin per 100 c.c. of blood. The large amounts of blood necessary to maintain this level in N. P. before operation suggest increased blood destruction, although the destruction was not reflected by an increased iron excretion in the urine or an elevation of the Van den Bergh. The former was performed on four successive occasions. Further, the deposits of iron pigment in the liver and spleen were not sufficient to account for all of the iron which was being liberated by the destroyed cells. The inference seemed to be that the breakdown products of the red cells were being promptly utilized within the body for new blood formation.

#### SUMMARY

The observations on the striking good effect of splenectomy on identical twins suffering from erythroblastic anemia of Cooley are recorded.

The twins following splenectomy required only one-third to one-fifth the amount of blood to maintain a level of 5 Gm. hemoglobin (critical level) per 100 c.c. of blood than before operation. Both children made substantial weight gains and were greatly improved symptomatically following the operation.

#### REFERENCES

1. Cooley, T. B., and Lee, P.: *Tr. Am. Pediat. Soc.* 37: 29, 1925.
2. Cooley, T. B., Witwer, E. R., and Lee, P.: *Am. J. Dis. Child.* 34: 347, 1927.
3. Baty, J. M., Blackfan, K. D., and Diamond, L. K.: *Am. J. Dis. Child.* 43: 667, 1932.
4. Custer, R. P.: *Brennemann's Practice of Pediatrics*. McQuarrie. Hagerstown, 1945.
5. W. F. Prior Company, Inc., vol. 3, p. 11.
6. Hitzrot, J. M.: *Ann. Surg.* 88: 361, 1928.
7. Cooley, T. B., and Lee, P.: *Am. J. Dis. Child.* 43: 705, 1932.
8. Whipple, A. O., Reeves, R. J., and Cobb, C. C.: *Ann. Surg.* 88: 380, 1928.
9. Bradford, W. L., and Dye, J.: *J. PEDIAT.* 9: 312, 1936.
9. Connors, J. F.: *Ann. Surg.* 88: 385, 1928.

## ERYTHEMA MULTIFORME

### WITH SPECIAL EMPHASIS ON POSTVACCINAL ERYTHEMA

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THE etiology of erythema multiforme remains unknown, although many theories as to its origin have been advocated, such as toxic, bacterial, virus, or allergic factors. At times this syndrome seems to appear spontaneously without any associated illness. However, various observers have noted that this symptom complex may be associated in some instances with herpes simplex,<sup>1</sup> sulfonamide sensitivity,<sup>2</sup> Vincent's infections, rheumatic fever, and occasionally with smallpox vaccination.<sup>2-6</sup>

During the period from July to December, 1945, we have had the opportunity of observing three cases of erythema multiforme with involvement of the skin and mucous membrane following smallpox vaccination. Coincident involvement of skin, oral mucosa, and the conjunctivae has been termed the Stevens-Johnson syndrome. Murphy<sup>7</sup> has suggested that this syndrome should be separated from erythema multiforme in which no changes of the mucous membrane are found, but this appears to be a matter of definition, as the pathogenesis is probably the same. Also, we are reporting three other cases of erythema multiforme of seemingly diverse etiology. One such case was associated with acute rheumatic fever, one followed the administration of horse serum, and one case had no discernible etiologic factor.

*Postvaccinal Rashes. Review of the Literature.*—Smallpox vaccinations are occasionally followed by skin eruptions of various types. Bloch<sup>6</sup> classifies these eruptions as: (1) papular; (2) urticarial and erythematous, including papular urticaria, erythema multiforme, morbilliform erythema, scarlatiniform erythema, roseola, urticaria, erythema iris, nummular erythema, erythema, and red urticaria; (3) purpuric petechial; (4) pustular, including bullous impetigo, folliculitis, pustular erythema, exfoliative dermatitis; (5) eczematoïd. Heaton<sup>8</sup> reports a purpuric rash following vaccination, as do Davidson and Davis.<sup>9</sup> Chalke<sup>10</sup> describes rashes of papular type, morbilliform and maculopapular lesions subsequent to vaccination. The cause of some of these rashes is occasionally obvious, such as the spread of vaccinia virus to the surrounding skin by scratching, or generalized spread as may occur in the presence of eczema. On the other hand, the cause of lesions of the skin and mucous membrane such as appear in erythema multiforme is not known. Eichenlaub<sup>3</sup> suggests that the etiologic factor may be a foreign protein in the vaccine or in the cowpox virus itself, or some antitoxin produced by the body. Chalke<sup>5</sup> attempts to explain this type of rash as due to absorption either of toxic products from the vaccinal pustule, or of the lymph of the vaccine. Ricketts and Byles, to

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quote Bloch,<sup>6</sup> attribute the erythematous lesions to circulation in the blood stream of secondary products of inflammation absorbed from the pustule, and regard the particulate eruptions as toxemic and not implying generalized spread of the specific virus. Davidson and Davis offer an allergic tendency as a possible explanation for these vaccinal reactions.

**Incidence.**—The incidence of erythema multiforme following vaccination must be exceedingly small. Almost every patient who enters the San Francisco Hospital is routinely vaccinated (approximately 14,600 admissions a year), and yet we can find no record of the occurrence of erythema multiforme in any patients except those reported here. Sobel<sup>11</sup> found 80 cases of generalized eruptions in 4,160 vaccinations. Eichenlaub<sup>3</sup> reported only one case of generalized dermatosis in 10,000 vaccinations. Director<sup>4</sup> described one case of postvaccinal exanthem among 122,000 vaccinations. Among one-half million vaccinations, Bloch<sup>6</sup> found 123 regional or general eruptions. Of the 123, twenty were erythema multiforme, and four were erythema iris. Chalke reported 14 children with eruptions among 1,600 vaccinated.

Erythema multiforme may follow primary or revaccinations. Of our three patients, two suffered from the disease following an initial vaccination, and one following revaccination. This last was a vaccinoid reaction.

#### CASE REPORTS

**CASE 1.**—R. O., aged 17 months, white, male, entered the San Francisco Hospital with the complaint of a rash of two days' duration. He had been successfully vaccinated ten days prior to entry. Two days before entry some "red marks" were noted on the left shoulder, upper left arm, and behind the left ear. Soon afterward larger red blotches appeared over the upper trunk and neck. The eruption behind the ear bled, but the others did not. The child became feverish and irritable and refused everything by mouth. The family physician noted lesions in the mouth the day before hospitalization but no treatment was given. Past history disclosed only an attack of chickenpox several months previously.

Examination revealed the rectal temperature to be 99° F. The child was very irritable. Pleomorphic skin lesions varying from pustules to discrete and confluent irregular maculopapules were noted on the face, especially the forehead, the neck, shoulders, back, and upper left arm. The cervical and axillary lymph nodes were enlarged. Purulent nasal discharge was present. The lips were dry and puffy. The gums and tongue were normal. The buccal mucosa was covered by large bullous lesions which were easily ruptured, leaving a purulent exudate on the tongue blade. The pharynx and tonsils were normal. The remainder of the physical examination was negative except for a crusted vaccination lesion.

**Laboratory studies:** The urine was normal. The hemoglobin was 10 Gm.; red blood cell count, 4,750,000; white blood cell count, 24,800, with 67 per cent neutrophils of which 10 per cent were nonfilamented, 5 per cent eosinophiles, 1 per cent basophiles, 25 per cent lymphocytes, and 2 per cent monocytes. The Wassermann reaction was negative. The sedimentation rate (Wintrobe method) was 2 mm. per hour, corrected.

The patient remained afebrile and improved rapidly on symptomatic therapy, including vitamins and iron, and was discharged as well on the sixth day of hospitalization.

**CASE 2.**—L. G., aged 15 months, white, female, entered with the complaint of a sore mouth of one day's duration. Two days before entry the child was fretful and slept poorly. On the following day the child's face became swollen and she refused to eat. On the day of entry, the mother noted bleeding and discharge from the mouth. The child had been vaccinated successfully twelve days before the onset of these symptoms. The child was known to be sensitive to wheat, egg, and orange.

Examination revealed the rectal temperature to be 101° F. The child was fretful and appeared quite ill. A macular and maculovesicular rash was noted generally over the body from the hairline to the ankles. The lesions were small, bronze in color, and of uniform size. On the left arm was a crusted vaccination lesion. The angles of the mouth were fissured and bleeding. The gums were spongy and bled easily when touched. On the buccal mucosa were large, white, sloughing patches which bled on pressure. The pharynx was very injected, but no exudate or membrane was present. The remainder of the physical examination was negative.

Laboratory studies: The urine was normal. The hemoglobin was 16 Gm.; red blood cell count, 5,150,000; white blood cell count, 22,000, with 75 per cent neutrophils of which 10 per cent were nonfilamented, 2 per cent eosinophils, and 23 per cent lymphocytes. Smears of the mouth were negative for fusiform bacilli and spirochetes, as were cultures for streptococci and diphtheria. Under treatment with mouthwashes of sodium perborate the lesions cleared rapidly. The child was afebrile in twenty-four hours and was discharged after six days.

CASE 3.—J. B., aged 9 years, white, female, was referred to the hospital with the diagnosis of probable diphtheria. She had been vaccinated for the second time ten days previous to entry. Three days later she developed coryza. Three days afterward sore throat and wheezing appeared. Her physician had prescribed sulfonamide but she had consistently vomited the drug. Two days before entry, eight days after vaccination, her face became puffy and her lips began to swell. The day preceding hospitalization her gums started to bleed and her "mouth started to slough and her breath became foul." The patient developed difficulty in swallowing and marked dyspnea. The latter was relieved by subcutaneous epinephrine. Past history disclosed the occurrence of pertussis and rubella in early childhood, and asthma of several years' duration. She had been vaccinated successfully at 10 months of age.

Examination revealed the rectal temperature to be 104° F. The child appeared acutely and severely ill. On the trunk and extremities were large, red, raised lesions which were entirely discrete but variable in size. A healing vaccination was noted on the left arm. The eyelids were swollen and red and the conjunctivae were markedly injected. In addition, several small subconjunctival hemorrhages were present in the right eye. The breath was foul. The lips were swollen, crusted, and bleeding. Small patches of a grayish membrane were seen over the gums, buccal mucosa, and pharynx. Squeaks and groans were heard throughout both lung fields, but no râles or changes in percussion note were found. The remainder of the physical examination was normal.

Laboratory studies: The urine was normal. The hemoglobin was 94 per cent; red blood cell count, 4,150,000; white blood cell count, 12,000, with 62 per cent neutrophils of which 2 per cent were nonfilamented, 2 per cent eosinophils, 36 per cent lymphocytes. The Wassermann reaction was negative.

The patient remained in the San Francisco Hospital for only twenty-four hours, and was then transferred to private care. Inquiry later revealed that she had made a complete recovery.

This patient had a history of sulfonamide ingestion, but had supposedly vomited each dose. Fletcher and Harris<sup>2</sup> report three cases of erythema multiforme possibly caused by sulfonamides. We feel that the sulfonamide probably played no part in this patient's illness.

CASE 4.—F. W., aged 18 years, white, female, developed a sore throat and mouth five days before entry. The following day she felt weak and developed a fever which persisted. The patient had had similar attacks of sore mouth previously and had been told by her physician she was allergic to cats. After giving her cat away she had no further difficulty until the present illness. The day before entry a blister with a red border appeared on her nose. The lesions spread over her face and then the rest of her body. For eight

weeks preceding hospitalization the patient had experienced frequent nosebleeds. Past history revealed that she had had an episode of fever and joint pains at the age of 11 years, but nothing similar since. In addition she had had measles, chickenpox, pertussis, and mumps.

The rectal temperature was 105° F. The patient appeared acutely ill and uncomfortable and exhibited a moderate degree of dyspnea. The conjunctivae were markedly injected. The lids were covered with a discrete rash characterized by a small bleb surrounded by a bright red border. A diffuse eruption was present all over the body, but was most intense on the face. The lesions were vesicles surrounded by a bright red areola. The lips were cracked, oozing purulent material. The entire mucosa of the mouth was covered with a grayish membrane which wiped off easily, leaving a bleeding surface. The gums were purplish with a slight exudate about the margins. The pharynx was covered with the same type of membrane found in the mouth. Coarse, dry rhonchi were heard at both lung bases, and a friction rub was noted at the left base. The heart rate was 140 per minute. The heart was of normal size to percussion. The pulmonic second sound was accentuated. A soft apical systolic murmur was present. The remainder of the physical examination was negative. The clinical impression was acute rheumatic fever with erythema multiforme.

Laboratory investigation revealed the urine to be normal on repeated examinations. The hemoglobin was 14 Gm.; red blood cell count, 4,700,000; white blood cell count, 11,000, with 81 per cent neutrophils, 1 per cent eosinophils, 1 per cent basophils, 13 per cent lymphocytes, and 4 per cent monocytes. Repeated blood counts were gradually nearer normal. The Wassermann reaction was negative. Cultures from the skin lesions failed to grow. Cultures of the sputum revealed hemolytic staphylococcus aureus, streptococcus viridans, and other organisms of the oral flora. The serum albumin was 3.16 Gm. per cent; the globulin 2.14 Gm. per cent. Icterus index was 7.2 units. The nonprotein nitrogen was 45.4 mg. per cent; one week later it had declined to 35.4 mg. per cent. Roentgenologic examination of the chest on entry showed the left border of the heart to be straight, suggesting mitral valve disease. Mottled areas of increased density were present throughout the lung fields. A chest film two weeks later showed a heart of mitral configuration but not enlarged grossly. The lungs were then clear. Serial electrocardiograms were obtained. The initial record, shortly after entry, revealed a sinus tachycardia of 136 per minute. There was slight tendency to right axis deviation. P-R interval was 0.12 seconds. P<sub>2</sub> and P<sub>3</sub> were tall and peaked. T<sub>1</sub> was flat. ST<sub>2</sub> was depressed and T<sub>2</sub> was flat. T<sub>3</sub> was low. Succeeding records showed a gradual reversal until all T-waves were normally upright.

Intravenous phenolsulfonphthalein excretion was 75 per cent in one hour. Arm-to-tongue and arm-to-lung circulation times were 11 and 6 seconds, respectively. Sedimentation rates gradually declined from an initial high level to near normal on discharge to convalescence.

During the first week in the hospital a septic fever reaching as high as 105° F. daily continued, but then declined by lysis. The chest gradually cleared and the patient was discharged after forty days.

CASE 5.—I. F., aged 21 years, white, female, entered with a history of a sore throat of three days' duration and a rash for one day. Except for one episode of vomiting, she had no other symptoms. Past history revealed the occurrence of measles, chickenpox, and pertussis.

Physical examination disclosed the rectal temperature to be 100° F. The throat was very red and a slight amount of exudate was present. A typical scarlatiniform rash was noted, maximal in the skin folds. There was an early "strawberry" tongue. The remainder of the physical examination was negative.

The urine was normal. White blood cell count was 8,400, with 70 per cent neutrophils. Throat culture revealed nonhemolytic streptococcus.

A Schultz-Charlton test was applied and the area blanched. Seven days after administration of the horse serum used in the blanching test, a number of macular erythematous areas appeared over the extremities. These increased in number the following day,

and redness and swelling of the small joints of the hands and feet were noted. An electrocardiogram was normal. The skin lesions and joint manifestations disappeared in two days and the patient was discharged with the diagnosis of scarlet fever, and erythema multiforme and multiple arthritis due to horse serum.

CASE 6.—F. C., aged 3½ years, white, male, entered San Francisco hospital with a history of cough and coryza of 10 days' duration. Three days before entry the patient developed a fever, and on the day preceding hospitalization a rash appeared on the abdomen and spread rapidly over the body. The past history was irrelevant.

Physical examination revealed an acutely ill child whose rectal temperature was 103° F. Respirations were rapid and the child coughed frequently. A fading maculopapular rash which was hemorrhagic in some areas was present over the face, trunk, and extremities. There were several ulcerated areas on the buccal mucosa, 3 to 4 mm. in size, but no Koplik's spots were noted. The throat was red and considerable purulent postnasal discharge was seen. Crepitant râles were heard throughout both lung fields. The remainder of the physical examination was negative.

Transient acetonuria was the only abnormal urinary finding. The white blood cell count was 25,000, with 56 per cent neutrophils.

The patient became afebrile in three days following the administration of sulfadiazine. The lesions of the skin and of the mucous membrane cleared. No possible cause for the multiform lesions could be demonstrated at any time.

#### DISCUSSION

While no definite proof of the etiology of the syndrome of erythema multiforme is available, it seems probable from our data that some allergic phenomenon, or, rather, an antigen-antibody reaction is the cause. Cases 2, 3, and 4 give a past history of allergy. In the instance of the patient discussed in Case 4, who had rheumatic fever, it seems likely that the erythema multiforme was, in common with the carditis, a manifestation of streptococcal sensitivity. The patient of Case 5 had received horse serum and the multiform rash, like the joint manifestations, probably represented serum sickness.

Since the virus is disseminated early in the course of vaccinia, and since toxic absorption might be considered maximal during the stage of pustulation, the late occurrence of postvaccinal erythema multiforme is most compatible with an allergic phenomenon.

In four of our six patients, the mucous membrane lesions of the mouth, and, to a lesser degree, those of the conjunctivae, were so striking and so unlike any other lesions, that they probably can be considered pathognomonic of erythema multiforme.

Three of our patients, Cases 3, 4, and 6, presented chest findings suggestive of a diffuse pneumonitis. Sputum cultures in Case 4 revealed only organisms of the oral flora. It seems likely that this pulmonary process might be due to lesions similar to those seen in the mouth.

#### SUMMARY

1. Erythema multiforme may occur as an infrequent complication of small-pox vaccination.

2. The occurrence of erythema multiforme following vaccination, horse serum administration, and during rheumatic fever, together with the high inci-

dence (50 per cent) of an allergic history, suggests that the disease represents an allergic reaction.

3. The mouth lesions of this syndrome are so unique as to be diagnostic.
4. Pneumonitis is of frequent occurrence in erythema multiforme.

#### REFERENCES

1. Anderson, N. P.: Arch. Dermat. & Syph. 51: 10, 1945.
2. Fletcher, M. W. C., and Harris, R. C.: J. PEDIAT. 27: 465, 1945.
3. Eichenlaub, F. J.: South. M. J. 19: 186, 1926.
4. Director, W.: U. S. Nav. M. Bull. 42: 884, 1944.
5. Chalke, H. D.: Lancet 1: 578, 1931.
6. Bloch, E.: Lancet 2: 504, 1942.
7. Murphy, R. C., Jr.: New England J. Med. 230: 69, 1944.
8. Heaton, T. G.: Canad. M. A. J. 43: 593, 1940.
9. Davidson, L. S. P., and Davis, L. J.: Lancet 2: 103, 1943.
10. Chalke, H. D.: J. Roy. Army M. Corps 77: 254, 1941.
11. Sobel, J.: Med. News 77: 199, 1900.



## A CASE OF ERYTHROBLASTOSIS FETALIS CAUSED BY ISOIMMUNIZATION WITH THE AGGLUTINOGEN B

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**E**RYTHROBLASTOSIS fetalis is an antigen-antibody disease of the newborn which may occur unrelated to the Rh factor. It may result from the isoimmunization of an Rh-positive, type O mother whose baby is either type A or type B, and a specific increase in the normally present isoagglutinin titer of the mother's blood may be taken as confirmatory evidence of such isoimmunization.

Levine,<sup>1</sup> in an early review of the pathogenesis of erythroblastosis fetalis, stated that the disease is caused by isoimmunization of the mother by a dominant hereditary blood factor in the fetus, which was the Rh factor in more than 90 per cent of the cases. He postulated that the remainder of the cases might be induced by the factor A or B in the fetal blood. More recently, Halperin and associates<sup>2</sup> indicated that such might be the case when the mother was type O and the baby type A. Polayes and Ohlbaum<sup>3</sup> have demonstrated nine cases where the Rh factor as well as the Hr antigen were excluded as possible immunizing antigens and all of the children were type A and their mothers type O, with high anti-A agglutinin titers in the mothers' serum.

To date there have been no reports in the literature of a specific case in which the erythroblastotic infant was type B and the mother Rh-positive, type O, with an elevated anti-B agglutinin titer in the mother's serum. The purpose of this communication is to report such a case.

### CASE REPORT

L. B., a 7 pound, 2 ounce full-term, white male, was born Dec. 26, 1945. The infant was apparently normal at birth, but within twenty-four hours was markedly icteric and the liver was enlarged to one and one-half fingerbreadths below the costal margin. Study of the peripheral blood showed the typical findings of erythroblastosis fetalis. Transfusion was temporarily delayed because of the high hemoglobin value and the high red blood cell count, but the following day these findings were lower and the baby had lost 4 ounces. The infant was given a transfusion of 75 c.c. of whole citrated blood. There was a good hematological response to the transfusion and he maintained his weight. It was necessary to give him an additional transfusion on the sixth day of life because of a second fall in the red cell count. (Table I.) He made an uneventful recovery from his erythroblastosis fetalis and was discharged on his eighth day of life. He was only faintly jaundiced and the liver was no longer palpable at that time. The peripheral blood on discharge was that of the normal newborn. He is now alive and is completely normal in every respect.

Complete examination of the blood of the mother, father and baby revealed:

Father: Group B N, Rh-positive, group Rh, Hr positive

Baby: Group B N, Rh-positive, group Rh, Hr negative

Mother: Group O MN, Rh-positive, group Rh,

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Examination of the serum of the mother showed no anti-Rh agglutinins, and no anti-Hr agglutinins. There were no blocking antibodies. The result was negative when tested by the conglutinin method.

The mother's serum, however, showed agglutinins against A<sub>2</sub> cells in titer of 25, and against B cells in titer of 100. When tested by the conglutinin method against A<sub>2</sub> cells the titer was 50, and against B cells the titer was 400.

TABLE I. HEMATOLOGICAL COURSE OF INFANT L. B.

DAY OF LIFE	NUCLEATED RBC PER 100 WBC	HEMOGLOBIN IN GRAMS	ERYTHROCYTES	LEUCOCYTES
1	27	16.0	5,320,000	32,000
2	5	14.0	4,580,000	32,000
3	7	15.0	4,490,000	23,000
4	3	17.5	4,720,000	17,650
5	1	14.5	3,330,000	16,250
6	2	14.0	3,630,000	15,650
7	2	17.5	5,360,000	13,450
8	1	18.0	4,500,000	19,000

## SUMMARY

A case of erythroblastosis fetalis caused by isoimmunization of an Rh-positive, type O mother by a type B baby is reported with confirmatory blood serologic findings.

It is suggested that when an erythroblastotic infant is seen, whose mother is type O and her Rh factor is unknown, the baby be transfused with type O, Rh-negative blood. This would obviate the possibility of giving the infant blood to which he has circulating isoagglutinins.

We are indebted to Dr. Lester J. Unger, Director of the Blood Transfusion and Plasma Division of the New York Post-Graduate Medical School and Hospital, for the complete study of the blood of this family.

## REFERENCES

1. Levine, P.: J. PEDIAT. 23: 656, 1943.
2. Halperin, J., Jacobi, M., and Dubin, A.: Am. J. Obst. & Gynec. 50: 326, 1945.
3. Polayes, S. H., and Ohlbaum, C.: Am. J. Clin. Path. 15: 467, 1945.

# TRANSFUSION OF VERY SMALL INFANTS UTILIZING PNEUMATIC PRESSURE

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COMMON difficulties of transfusing tiny infants, such as sticky syringes, intermittent flow, variation of force applied to the plunger, air bubbles getting into the line, and accidental yanking of the needle out of the vein, are obviated by employing air pressure as an impelling force. This arrangement affords all the advantages of gravity with less than a foot of small caliber blood-count-pipette rubber tubing, and using as small calibered needle as desired.

The method can furthermore be employed in infusions by bone-marrow route or otherwise when the rate of flow needs to be accelerated, but at the same time controlled.

A sphygmomanometer is utilized to provide the compressed air. Either mercury or aneroid type will do. By insertion of a Y or T tube in the line from the bulb to the rubber arm cuff, air under any desired degree of pressure may be conducted through a stopper into the top of the blood reservoir, there to exert a continuous, even, controllable force for driving the blood into the vein.

The rate of flow is adjusted by raising or lowering the mercury; 4 to 5 c.c. per minute is best. At this rate, the baby's circulation can accommodate a maximum quantity of blood or saline suspension of cells with a minimum danger of cardiac distention. As much as 15 c.c. of whole blood (or 20 c.c. of saline suspension of cells) per pound of body weight have been given with no reaction.

A 22 gauge needle delivers at this rate most satisfactorily.

The sphygmomanometer may rest on the tray of a Mayo stand, while the blood reservoir and its subjacent filter-drip are suspended from the projecting rim of the same stand (or from a standard close by) at just such a height that two inches of small caliber rubber tubing will connect with a 3-way stopcock on the table, and six inches more tubing leading to a glass observation tube and suitable needle will complete the conducting system to the baby. A 10 or 20 c.c. syringe for saline solution occupies the extra inlet to the 3-way stopcock.

As a blood reservoir I find the barrel of a 100 c.c. syringe, closed with a No. 8 one-hole stopper convenient. Its accurate calibration recommends it particularly. A commercial bottle such as the transfuso-vac can be used, however, by adding, at the base of the Y tube, a rubber tube leading to a needle adapter and a 20 gauge needle which is inserted through a prepared thin spot in the rubber stopper, into the air-admitting glass tube which is part of the apparatus. Steps in the use of the apparatus follow:

1. Fill syringe with saline and attach to 3-way stopcock.
2. Turn stopcock to connect saline syringe with filter-drip, and run saline up the tube and into the bottom of the drip glass to a height of about  $\frac{3}{8}$  inch.

3. Turn stopcock to connect saline syringe with intravenous needle and run saline through till it drips from the intravenous needle.

4. Pour blood into container and insert cork tightly; (or if the commercial bottle is used, insert air-line needle into its aperture in the stopper).

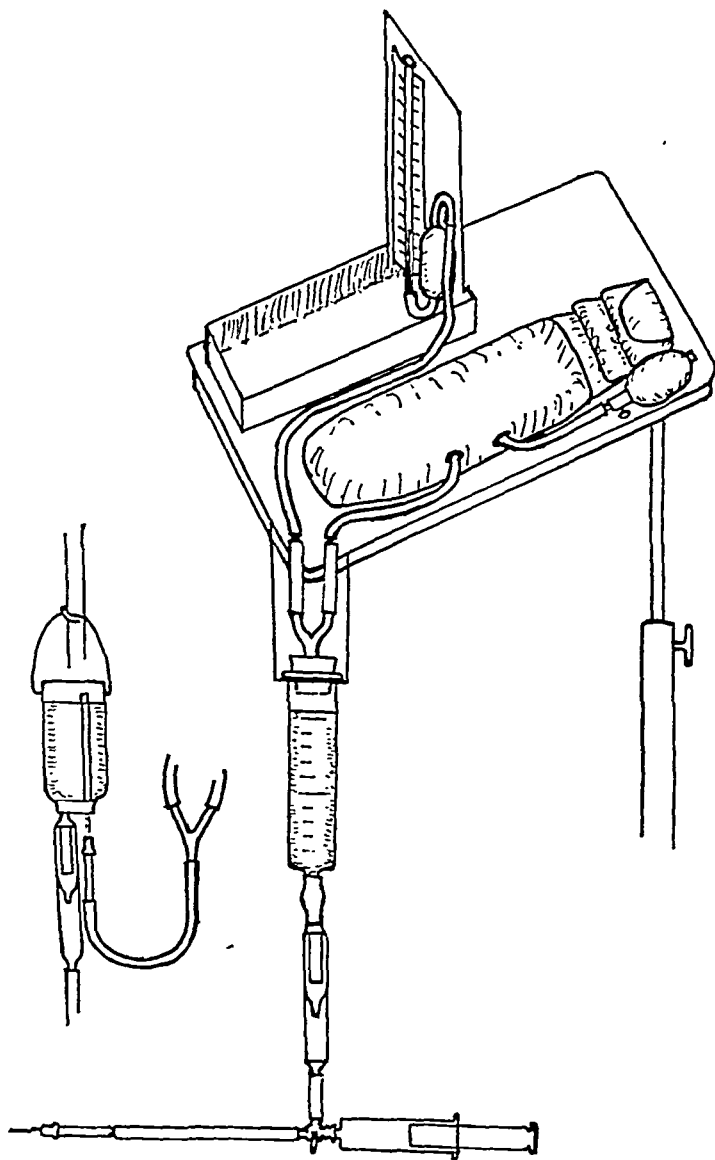


Fig. 1.

5. With sphygmomanometer valve closed, pump pressure up till it reaches and rests at 50 mm.

6. Apply tourniquet.

7. Insert needle in vein, by direct venepuncture if possible—by cut-down and tie-in if necessary.

8. Assure presence of needle in vein by withdrawing slightly on saline syringe.

9. Remove tourniquet.

10. Assure discharge of needle into vein by injecting a few c.c. of saline.

11. Turn stopcock to connect blood with needle.

12. Increase air pressure as necessary till flow is 4 to 5 c.c. per minute, and regulate from time to time to keep flow at this rate. (This has been found to vary according to size of needle used, position in vein, resistance of baby and other factors from 50 mm. up to as high as 120.)

13. Stop the flow not later than when the last drop of blood reaches the observation tube so that air is not blown into the vein.

If trouble develops at the needle:

1. Turn stopcock to stop blood flow and connect saline syringe with needle.

2. Withdraw needle from vein, and insert it in saline solution.

3. With syringe draw saline up through needle till observation tube contains saline instead of blood.

4. Adjust air pressure to 50 mm.

5. Repeat previous procedure beginning at No. 6.

# The Academy Study of Child Health Services

## THE SECOND YEAR OF THE STUDY BEGINS WITH TWO CAMPAIGNS AHEAD

As the first year of active progress in the Study of Child Health Services draws to a close, the time has come to take stock of the pre-ent situation and to outline for members of the Academy the general plan of action for the coming year.

As of September first, state programs have been successfully organized in all but one of the forty-eight states, including the District of Columbia and the Territory of Hawaii. In addition to the original pilot study in North Carolina, five states have completed the data-collection phase of their programs, and several others are rapidly approaching this stage. In the relatively small number of states in which the distribution of the questionnaire schedules has not been completed, it is anticipated that this phase of the Study as well as the collection of the data will be accomplished within the next few months. Thus the end of the calendar year should find this initial phase of the Study complete on a nationwide scale. With the final stages of the state programs in sight, the Central Executive Staff has been developing its activities primarily along two main lines: the statistical analysis of the material gathered in the states and the development of that part of the Study concerned with an evaluation of pediatric education.

### STATISTICAL ANALYSIS

In anticipation of the volume and significance of the work now confronting us, the statistical division of the Central Executive Staff has been greatly strengthened. On September 1, Mr. Rollo Britten was appointed a full-time member of the executive staff. Mr. Britten has been giving half time to the Study since June, 1945, dividing his time between the Academy Study and the Commission on Hospital Care. Now, having been relieved of all other responsibilities, he has been appointed by the director and paid from Academy funds in order to take charge of the statistical division of the Study. In view of his many years' service as statistician with the U. S. Public Health Service, and by virtue of his experience as chief analyst of the results of the National Health Survey, Mr. Britten is particularly well qualified for this most important assignment.

One of the aspects of the statistical work which is now receiving increased emphasis is the reviewing, correcting, and, in so far as is possible, completing of the information requested on the questionnaire schedules. No matter how strong the statistical team at the Central Office, the value of the results will be limited by the diligence and accuracy with which these data are collected and reported by the state executive secretaries. To supervise this work and to assist the executive secretaries in this important aspect of the Study, Mrs. Mary Hubbard was added to the central staff in August. Mrs. Hubbard's first activity as a staff member will take her on tours throughout the states in order that she may assist the executive secretaries in giving maximum value to the completed questionnaires before they are sent in to the Central Office.

As the statistical division of the Study staff is growing rapidly, a greatly expanded office is planned to accommodate the increase in personnel required. In order to accomplish the tremendous amount of statistical labor within the shortest possible time, it is expected that an additional fifty or sixty full-time editors and coders will be needed during the coming winter. Supervision of the technical force will be in the hands of Miss Regina Lowenstein, another newcomer to the staff, who has had extensive statistical experience.

In the August issue of the JOURNAL OF PEDIATRICS, this column contained a description of preliminary plans for three regional meetings to be held during September in Chicago, San Francisco, and Washington. These meetings have grown out of the fact that state chairmen have expressed to us in the Central Office their feeling of a need to discuss with the

executive staff the question: What are the states going to get out of this Study? State chairmen, executive secretaries, and state committees have put so much effective effort, time, and money into collecting the desired information that increased emphasis has been given to the importance of suitable reports to be written for each State. It has appeared essential, therefore, to provide, as soon as possible, an opportunity for the executive staff to obtain from state groups a more definite and detailed expression of their opinions, and at the same time to give to these state groups some idea of the statistical limitations of the Study, together with a description of the tabulations now being prepared. For this purpose a first draft of an outline covering the main topics to be included in reports of the Study at both national and state levels has been drawn up for presentation and discussion at the meetings. Questions pertaining to each of the major topics are included in the outline and the tentative analytical table forms to be used in answering the proposed questions will also be presented. Judging from the enthusiastic response with which the original plan for these three meetings was received, all three sessions promise to produce spirited discussion and exchanges of opinion. Copies of the outline have been distributed to all persons planning to attend the meetings, in order that they may be prepared to make suggestions, additions, and other pertinent comments concerning the proposed content of the state reports. After these meetings have taken place, a full report of them will be presented in the November issue of the JOURNAL OF PEDIATRICS.

#### STUDY OF PEDIATRIC EDUCATION

This important phase of the Study concerning the character and scope of pediatric training in medical schools and teaching hospitals is to be conducted during the academic year 1946-1947. By this time it is anticipated that medical school curricula will have returned sufficiently to normal to permit a fair evaluation of pediatric education. Plans for this portion of the Study have been developed gradually during the past winter and summer and will be put into operation at an early date.

Dr. James L. Wilson, Professor of Pediatrics of the University of Michigan, has been appointed chairman of the subcommittee under whose direction the study of pediatric education is to be conducted. This committee is made up entirely of professors of pediatrics and chiefs of pediatric departments chosen from various sections of the country so that each member of the committee can be responsible for an area including approximately ten medical schools, thus covering all sixty-eight medical schools in the U. S. A. . The members of this committee and the medical schools assigned to them are as follows:

DR. JAMES L. WILSON, Chairman. Professor of Pediatrics, University of Michigan Medical School.

#### MEDICAL SCHOOLS

Wayne University College of Medicine, Detroit, Mich.  
 University of Michigan, Ann Arbor, Mich.  
 Western Reserve University School of Medicine, Cleveland, Ohio  
 University of Buffalo School of Medicine, Buffalo, N. Y.  
 University Rochester School of Medicine, Rochester, N. Y.  
 Syracuse University College of Medicine, Syracuse, N. Y.  
 University of Pittsburgh School of Medicine, Pittsburgh, Pa.  
 Ohio State University College of Medicine, Columbus, Ohio  
 University of Cincinnati College of Medicine, Cincinnati, Ohio  
 University of Louisville, Louisville, Ky.  
 Indiana University School of Medicine, Indianapolis, Ind.

DR. HENRY G. PONCHER. Professor of Pediatrics, University of Illinois College of Medicine.

#### MEDICAL SCHOOLS

Loyola University School of Medicine, Chicago, Ill.  
 Northwestern University Medical School, Chicago, Ill.  
 University of Chicago School of Medicine, Chicago, Ill.

University of Illinois College of Medicine, Chicago, Ill.  
 University of Wisconsin Medical School, Madison, Wis.  
 Marquette University School of Medicine, Milwaukee, Wis.  
 University of Minnesota Medical School, Minneapolis, Minn.  
 State University of Iowa College of Medicine, Iowa City, Iowa  
 St. Louis University School of Medicine, St. Louis, Mo.  
 Washington University School of Medicine, St. Louis, Mo.  
 University of Kansas School of Medicine, Kansas City, Kan.  
 Creighton University School of Medicine, Omaha, Neb.  
 University of Nebraska College of Medicine, Omaha, Neb.

DR. SAMUEL LEVINE. Professor of Pediatrics, The Cornell University College of Medicine.

#### MEDICAL SCHOOLS

Yale University of Medicine, New Haven, Conn.  
 Columbia University, New York, N. Y.  
 Cornell University, Ithaca, N. Y.  
 New York Medical College, New York, N. Y.  
 - New York University College of Medicine, New York, N. Y.  
 Long Island College of Medicine, Brooklyn, N. Y.  
 Boston University School of Medicine, Boston, Mass.  
 Harvard Medical School, Boston, Mass.  
 Tufts College Medical School, Boston, Mass.

DR. RALPH V. PLATOU. Head of Department of Pediatrics, Tulane University of Louisiana, School of Medicine.

#### MEDICAL SCHOOLS

Southwestern Medical College, Dallas, Texas  
 Baylor University College of Medicine, Houston, Texas  
 University of Texas School of Medicine, Galveston, Texas  
 University of Oklahoma School of Medicine, Oklahoma City, Okla.  
 Louisiana State University School of Medicine, New Orleans, La.  
 Tulane University School of Medicine, New Orleans, La.  
 University of Arkansas School of Medicine, Little Rock, Ark.  
 University of Tennessee College of Medicine, Memphis, Tenn.

DR. ROBERT LAWSON. Assistant Professor of Pediatrics, Bowman Gray School of Medicine of Wake Forest College.

#### MEDICAL SCHOOLS

Meharry Medical College, Nashville, Tenn.  
 Vanderbilt University School of Medicine, Nashville, Tenn.  
 University of Virginia Department of Medicine, Charlottesville, Va.  
 Medical College of Virginia, Richmond, Va.  
 Duke University College of Medicine, Durham, N. C.  
 Bowman Gray School of Medicine, Winston-Salem, N. C.  
 Medical College of the State of South Carolina, Charleston, S. C.  
 Emory University School of Medicine, Atlanta, Ga.  
 University of Georgia School of Medicine, Augusta, Ga.

DR. FRANCIS SMYTH. Dean, University of California Medical School.

#### MEDICAL SCHOOLS

University of Oregon Medical School, Portland, Ore.  
 University of California Medical School, San Francisco, Calif.  
 Stanford University School of Medicine, San Francisco, Calif.



College of Medical Evangelists, Los Angeles, Calif.

University of Southern California School of Medicine, Los Angeles, Calif.

University of Utah School of Medicine, Salt Lake City, Utah

University of Colorado School of Medicine, Denver, Colo.

DR. WALDO NELSON. Professor of Pediatrics, Temple University School of Medicine.

#### MEDICAL SCHOOLS

Hahnemann Medical College, Philadelphia, Pa.

Jefferson Medical College of Philadelphia, Philadelphia, Pa.

Temple University School of Medicine, Philadelphia, Pa.

University of Pennsylvania School of Medicine, Philadelphia, Pa.

Woman's Medical College of Pennsylvania, Philadelphia, Pa.

John Hopkins University School of Medicine, Baltimore, Md.

University of Maryland School of Medicine, Baltimore, Md.

Georgetown University School of Medicine, Washington, D. C.

George Washington University School of Medicine, Washington, D. C.

Howard University College of Medicine, Washington, D. C.

A preliminary meeting of this committee was held in Washington, D. C., in June of this year at which time the first draft of the questionnaire schedules for this portion of the Study (Series IV) and the general plan of action were discussed. It was agreed that, in so far as circumstances allow, a visit should be made by the committee members to each medical school assigned to them together with one or more members of our Central Executive Staff. In this way the study of each school could include the opinions of an outstanding teacher of pediatrics plus those of a member of our staff whose past experience includes both practice and teaching and whose function would be to assure that in each school the same techniques of gathering information are used. In this manner a consistent and most interesting picture of pediatric education throughout the country should be obtained. Dr. John McKenney Mitchell has been designated as the member of the Central Executive Staff to serve as full-time director of this part of the Study. It may be that Dr. Mitchell will not be able to visit all of the medical schools during the coming year in which case other members of the executive staff will visit some of the schools and teaching hospitals.

JOHN P. HUBBARD, M.D.,

Director, Study of Child Health Services

# The Social Aspects of Medicine

## COMPULSORY PREPAID MEDICAL CARE\*

By W. A. MILLMAN, SECOND VICE PRESIDENT

THE EQUITABLE LIFE ASSURANCE SOCIETY

By the very nature of things there can be no precise and final division between governmental and private responsibilities for national health. These relationships are constantly changing and in recent years there have been remarkable advances in the science of medicine. These advances have been possible because there existed a spirit of initiative and freedom for experimentation. There is constant danger that, as governmental responsibilities are extended, inflexible patterns will be established, either by law or regulation, which will dampen the spirit of initiative and handicap experimentation. Consequently, whatever changes in the relationships between governmental and private responsibilities may be made in the future, it is of the utmost importance that we preserve these characteristics of the system of private enterprise.

### PUBLIC VS. PRIVATE RESPONSIBILITY

It is clear that government has primary responsibility with respect to certain activities essential to the health of the nation which, if they are to be performed effectively, must be handled by concerted action on the part of the community. On the other hand, the health and well-being of the individual is affected by a multitude of decisions and actions which are, and must necessarily be, the responsibility of the individual. Since the health of the nation must be measured in terms of the health of its individual citizens, many of the essentials of national health must remain in the domain of private responsibilities.

It is primarily in this field of joint responsibilities that there is disagreement as to the proper nature and extent of governmental participation. Specifically, there is sharp disagreement with respect to the nature of the responsibility which government should assume for the provision of medical, hospital and dental care for the self-supporting citizen and the extent to which government should assume responsibility for the continuation of the worker's income during periods of disability.†

### CRITICISM OF PRESENT SYSTEM

What do the proponents of compulsory health insurance seek to accomplish in this field of medical care? Their objectives seem to be concerned with the kind and the quality of medical care which the American public is now getting as well as with the cost of this medical care. It is claimed that not enough emphasis is placed on preventive care, that we do not have adequate facilities and personnel available for good medical care for all of the people, and that the facilities and personnel which we now have are not ideally distributed nor efficiently utilized. As to cost, it is claimed that good medical care is beyond the financial capacity of the majority of our citizens and that in any event these costs, because of their unpredictable incidence, frequently constitute financial catastrophes to the individuals who must pay the bills.

Much of this is true. The important question is, will the proposals for compulsory health insurance, such as those contained in the Wagner-Murray-Diagell Bills, S. 1606 and H. R. 4730, improve the situation? Many serious students of these problems have grave doubts on this point. Important among the reasons for these doubts are the following:

In the first place it is certain that many controls would be necessary both as to the manner in which the medical practitioners could practice their professions and as to the condi-

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†The latter will be treated by the author in a subsequent article.

tions under which eligible persons could avail themselves of medical services. These controls would probably be of such far-reaching character that they would result in unforeseen changes in the present bases of the practice of medicine. There has not been sufficient discussion of the necessity, under a plan of compulsory health insurance, for such controls, nor has adequate consideration been given to their probable consequences. While the proponents of compulsory health insurance have apparently given some consideration to these problems, they have not been frank with regard to these points with either the medical profession or the public.

#### CRITICISMS EXAMINED

As a result it is doubtful whether members of the medical profession would willingly participate in a plan of compulsory health insurance in sufficient numbers to enable it to achieve its objectives. Even if all of the present members of the medical profession should participate in and fully cooperate with the plan there are not enough doctors, dentists and nurses available to give the public the quality of care which it is entitled to expect and at the same time to furnish the amount of care which would be demanded if the factor of private financial responsibility were entirely removed.

President Truman and the Social Security Board have recommended that the Social Security Act be amended to include provision for medical care benefits. Senators Wagner and Murray, together with Representative Dingell, have, with the obvious approval of both the President and the Social Security Board, submitted to Congress a bill which would, among other things, provide such benefits. The remarks which follow will be based on the provisions of Title II of this bill relating to "prepaid personal health service benefits."

#### DIFFICULTIES UNDER COMPULSORY SYSTEM

Substantially the entire population of this country including both employees and their dependents would, under the terms of this bill, be entitled to medical, dental, nursing, laboratory and hospitalization benefits, subject to certain limitations. The cost of these benefits would, presumably, be met by a payroll tax upon both employers and employees. Responsibility for administration of this plan would be placed in the hands of the Surgeon General under the supervision and direction of the Federal Security Administrator. Provision is made for the establishment of an Advisory Council, appointed by the Surgeon General with the approval of the Federal Security Administrator. As its title indicates, the powers of this Council would be purely advisory.

The bill contains little specific detail as to administrative rules. Responsibility with accompanying broad authority would be vested in the Surgeon General to carry out the purposes of the bill in accordance with certain broad policies outlined in it. Because of the generality of these policies and the wide range of discretion given to these officials it is not possible to conclude from the bill alone what changes in the present system of medicine probably would result if this proposal became law.

It is, however, certain that a national health program such as proposed would cost a great deal of money. It is suggested that this cost would not be materially greater than the price now being paid by the American people for health care. Whether or not this is true the Surgeon General would have to keep the cost of the program within the limitations imposed by the revenues available. If abuses developed, abuses which cost money and threatened the solvency of the program, the Surgeon General would be forced to take steps to cure those abuses, or to limit their financial effect. Whether he seeks to cure the abuses by regulations limiting the conditions under which an individual can obtain medical service or regulations restricting or prohibiting certain medical practices, or whether he seeks to limit the financial effect of abuses by changing the basis of compensation of physicians and dentists, these regulations can, and probably would, fundamentally alter many features of the present system of medicine and medical economics.

The avowed purpose of the bill is to give everyone ready access to good medical care. The Surgeon General must, therefore, obtain the participation and the cooperation of the medical professions. Without that participation and cooperation, including that of the

more competent members of these professions, the plan would be an empty gesture. Whatever the justification for their attitude, the violent reaction of the organizations representing the major portion of the medical professions would indicate that such cooperation cannot be achieved at this time. Nor does it seem likely that their cooperation can be obtained in the future if there is a continuation of the lack of candor which has so far characterized the proponents of this type of legislation. The sort of cooperation which is necessary cannot be obtained by compulsion. If there is a reasonable basis for cooperation, obviously it can be best attained by a full and frank exploration of the necessary readjustments in the present system of medical care with such exploration made jointly by the advocates of such legislation and representatives of the moderate and conservative elements of the medical professions.

If the purposes of the bill are to be carried out more hospitals must be constructed and more doctors, dentists, nurses and technicians must be trained. President Truman has recommended financial assistance to the various States for the construction of more hospitals, and legislative proposals for this purpose are being given favorable consideration by Congress. But as the President pointed out, the building of additional facilities will not provide service. Service can be provided only by competent, well trained personnel. The training of such personnel will take both money and time. But, most important, it will take an adequate supply of competent young people willing to enter these professions. The effectiveness of any program to train more medical personnel will be affected by the attractiveness of these professions to the young people of our country from whom future doctors, dentists and nurses must be recruited.

Because it affects the attitude of the present members of these professions and the attitude of the potential future members, a most vital part of the program is the basis upon which those who render the service required under it will be compensated. The bill provides that the basis of compensation for general practitioners and dentists shall be determined by the majority of such practitioners in each local area with the right reserved to the Surgeon General to use a different basis of compensation for those who do not elect with the majority. It is well known that the majority of physicians in private practice today wish to continue the traditional fee-for-service basis of compensation for their services. It is with respect to this point particularly that the proponents of compulsory health insurance have lacked candor in dealing with the medical profession. While the bill provides that the doctors of any area may elect to continue to be paid on a fee-for-service basis, the principal proponents of this type of legislation, in a statement entitled "Principles of a Nation-Wide Health Program" published in November 1944, stated that:

*"The fee-for-service method is most open to abuse by patients and physicians and is the most costly to administer. Adequate control of the services requires fiscal and professional supervision, which is expensive and often vexatious. The promotion of quality and of prevention is difficult. The use of the fee-for-service method should therefore be discouraged, except for specialist services under certain conditions."*

What would be the result, then, if the Surgeon General must permit the doctors of each local area to choose a method of compensation which experts in the field agree will not work, and it appears that a majority of doctors will choose that method? One of the first steps might be to reduce the rate of payment for each unit of service so as to bring the over-all cost of services within the available funds. To reduce the pay of conscientious and competent physicians because of abuses by patients and by less conscientious physicians would be intolerable. The conscientious doctor, if he is to receive the compensation to which he is entitled, would be forced to make unnecessary visits and adopt many other undesirable practices followed by the physician who has abused the system. There would result an application of Gresham's law to the field of medical practices, with the bad driving out the good.

The next step might well be the abandonment of the fee-for-service method as a basis of payment to the general practitioner. The alternative bases of compensation contemplated

by the bill are payment to the general practitioner of a stipulated amount each year for each of his patients, the so-called capitation basis, or payment for the physician's services on a salary basis. These are, by and large, methods untried in this country in the field of general medical care. What effect they would have on the quality of medical care, its cost, and the attractiveness of the field of medicine to the present and the potential future doctors, dentists and nurses is practically unknown.

It might be observed, however, that the capitation method, under which the physician is paid the same amount each year regardless of the work he performs, opens at least two avenues for substantial abuse. In the first place it would be to the financial advantage of the individual physician to avoid taking patients who are apt to require a substantial amount of medical care. There are many ways in which the physician could select his patients for this purpose, and apparently he would be free to do so since the bill would permit the physician to reject individual patients. In the second place the general practitioner would find himself able to handle more patients, and hence to increase his income, if he made a habit of referring patients to specialists as soon as some minor complication arose. Other serious abuses are possible. Whether these abuses would become realities, or would prove to be purely imaginary, can more properly be determined by experimentation with voluntary plans rather than by adoption of a nation-wide compulsory plan.

What would be the result if a salary basis of compensating physicians were substituted for our present fee-for-service basis? Would professional standards be higher or lower than at present? Would the net change in the picture, including the introduction of political and bureaucratic forces, make the medical professions more or less attractive to qualified potential entrants into these professions? The recent disclosures concerning the medical care provided through the Veterans' Administration is disquieting in this connection. Certainly a careful examination of the character and quality of the services which are now being supplied by physicians employed on a salaried basis, including an investigation of the reasons for any shortcomings in the quality of that service, should be made before seriously considering adopting a national system which may force this as a general basis of compensation of physicians.

We have considered briefly the steps which might be taken for the purpose of limiting the financial effect of abuses by changes in the method of compensating physicians and other practitioners. Instead of attempting to limit the financial effect of abuses, the Surgeon General might attempt to avoid abuses by limiting the conditions under which an individual could avail himself of the services of a physician, dentist or hospital, or by restricting or prohibiting certain types of practices by physicians, dentists and hospitals.

Let us take a simple case by way of illustration. The Surgeon General might find that some physicians being reimbursed on a fee-for-service basis were making four, five or six visits for treatment of common colds where one visit would have been sufficient. In order to reduce the financial burden of this type of abuse he might decide that in any case diagnosed as a common cold the physician would not be allowed payment for more than two visits without specific approval of the case by a medical administrative officer. Obviously, it would be a simple matter to circumvent such a restriction by changing the diagnosis. Consequently, if the necessity for such restrictions and regulations should arise in practice, the variety of diseases and the diversity of medical practices would inevitably lead to a formidable volume of rules, regulations and report forms. Serious consideration should be given to the effect of such procedural problems on the ability of the physician to practice medicine efficiently and effectively.

The controls over the individual physician paid on a fee-for-service basis would arise from the necessity of the Surgeon General to limit costs. Use of a capitation basis or a salary basis has been suggested in order to avoid the problems of the fee-for-service basis. While these bases of compensation would be effective in limiting costs it is not clear that they would be effective in maintaining quality of medical care. Consequently, the controls which would be required under a salary basis or a capitation basis would probably be concerned with the problem of trying to assure a high quality of care, and would probably do so by detailed

regulations as to the precise manner in which the physician should practice medicine. Such a development would be accompanied by the grave danger that, by placing an administrative stamp of approval on currently accepted methods of treatment, new techniques and methods of treatment would be difficult to adopt, and might, in fact, be strangled by administrative red tape.

In addition to attempting to control abuses by adopting new methods of compensation, or by regulating the methods of practice by physicians, dentists and hospitals, the Surgeon General might have to limit the services which would be available under the proposed system. Such limitations are specifically contemplated by the Wagner-Murray-Dingell Bill. For instance it is obviously impossible for available personnel to furnish complete dental services to the entire population. Accordingly, the Surgeon General would be permitted to restrict the dental services to examination, diagnosis, prophylaxis, extraction and treatment of acute diseases of the teeth. Home nursing service and laboratory benefits might likewise be limited, because of restricted personnel and in order to control costs. In addition the Surgeon General would be authorized to require the payment of a fee with respect to the first service from a physician, dentist or nurse, or with respect to each service in a period of sickness or course of treatment.

One of the main objectives of those who propose compulsory health insurance is to obtain greater emphasis on preventive medical care. The Wagner-Murray-Dingell Bill recognizes, however, that sheer lack of available personnel, coupled with possible lack of funds, will limit that emphasis, and that abuses may arise which will necessitate barriers to such care. If our available personnel is limited, is it not possible that the abuses which will develop will divert the time and talents of that personnel to such an extent that less rather than more emphasis will be put on preventive care?

#### CONCLUSION

This suggests the thought that more progress in improving preventive medical care could be made by further emphasizing medical research, by improving facilities for medical education, and by expanding and improving our public health services than would result from adoption of such a far reaching and apparently unworkable plan as that contained in the Wagner-Murray-Dingell Bill.

There is need for the development of diagnostic centers. Such centers could be developed locally in association with hospitals, or otherwise, to make available on an efficient and economical basis the medical tools and knowledge already developed. These centers should be developed so as to supplement, not replace, the private medical practitioner. They could be financed in part by public funds or by private gifts and endowments, and in part by charges for services.

There is need for further development and experimentation with voluntary plans for prepayment of the costs of medical and hospital care. This development can be aided by the adoption of a more constructive attitude by the medical profession, by the insurance industry, and by employers. It is not suggested that the physician sacrifice those principles which he considers fundamental to the practice of good medical care, but there is room for him to adopt a more constructive and aggressive approach to the solution of the problems of the high cost of medical care. The individual physician should participate in the development of prepayment plans and should educate his patients to take advantage of prepayment plans.

There should be more experimentation with group practice as a foundation for plans for prepayment of medical costs. The individual physician should tolerate, even though he does not participate in, the development of such plans of group practice if they maintain proper medical standards.

## Academy News and Notes

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The following Fellows of the Academy have been discharged from the service:

### *Army*

Henry L. Barnett, New York, N. Y.  
Samuel S. Bernstein, Detroit, Mich.  
Charles W. Cory, Saginaw, Mich.  
Arthur J. Cramer, Jr., Buffalo (Kenmore), N. Y.  
Norman T. Crane, Plainfield, N. J.  
William V. B. Deering, Quincy, Ill.  
Frank H. Douglass, Seattle, Wash.  
S. Butler Grimes, Jr., Baltimore, Md.  
Ng William Hing, Puerto Rico  
Maurice W. Laufer, Riverside, R. I.  
Irving Le Bell, New York, N. Y.  
Newell L. Moore, Santa Ana, Calif.  
Marsh W. Poole, Klamath Falls, Oregon  
Irving Rosenbaum, Jr., Indianapolis, Ind.  
James B. Snow, Oklahoma City, Okla.  
Irwin P. Sobel, New York, N. Y.  
Martin L. Stein, Great Neck, N. Y.  
Maxwell Stillerman, Great Neck, N. Y.  
Joe M. Strayhorn, Nashville, Tenn.  
Hugh C. Thompson, Jr., Tucson, Ariz.

### *Navy*

Otto E. Billo, New York, N. Y.  
John H. Doval, Sacramento, Calif.  
Benjamin F. Feingold, Los Angeles, Calif.  
Herbert William Fink, Norfolk, Va.  
Robert N. Ganz, Boston, Mass.  
Robert S. McKean, Boise, Idaho  
Joseph F. Raffetto, Manasquan, N. J.  
Frederick P. Rogers, West Hartford, Conn.  
Edward A. Wishropp, Grosse Pointe Farms, Mich.

### *Canadian Navy*

Harry L. Bacal, Montreal, Quebec, Canada

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Lt. Herbert William Fink has been promoted from Lieutenant (j.g.) to Lieutenant in the Navy.

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Dr. Stanley D. Giffen, Toledo, Ohio, died on May 5, 1946. He was an Emeritus Member.

## Book Reviews

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**Government in Public Health.** Harry S. Mustard, M.D., LL.D., New York, 1945, The Commonwealth Fund, 219 pages. Price \$1.50.

This is an extremely interesting, authoritative, clearly written document which treats of contemporary public health work as a historical product. This approach, although it gives the social and political aspects of the subject rather than the scientific, the national aspects rather than the local, the general rather than the specific, enables one to view the present situation as a transition or trend.

Dr. Mustard points out that those preoccupied with public health organization and administration will not be satisfied with this approach; and he warns anyone who limits his knowledge of public health in the United States to what can be learned from this document that his information will be incomplete and that he will fail to "appreciate the fact that public health work in the United States is of a rather high order qualitatively." This reviewer believes, however, that no one could fail to benefit from this clear, concise presentation of so important a subject at this critical time.

The reader is introduced to the subject by an exposition of certain preliminary considerations such as the biologic and sociologic factors in health and disease, the character of public health problems, factors that express the seriousness of public health problems, factors that determine the make-up of a public health program.

Following these considerations, sixty-two pages are devoted to a discussion of the development of Federal Health Services. Of particular interest is the fact that Federal health work in the United States is not established as a coordinated health unit. In addition to the U. S. Public Health Service, about forty other Federal agencies participate to some degree in public health or medical care activities. Foremost of these are the Department of Agriculture, the Department of Commerce, the Department of the Interior, Federal Security Agency, and the Department of Labor.

As indicated before, emphasis is given to the social and political aspects of the development of the U. S. Public Health Service from the act of 1798, which provided compulsory health insurance for seamen, up to the present time. Throughout this discussion the actual phraseology used by members of the Congress relative to health organization is presented.

The following two chapters are devoted to the development, organization, expenditures, and source of funds of State and local health departments, with constant recognition of the fact that the bulk of actual health service is and must be rendered by local departments of health. It is emphasized that although each of the forty-eight states received some Federal assistance for health purposes, there remains about 25 per cent of the total population of the United States which does not come under the jurisdiction of organized local departments of health. The growth of local health work is indicated by the fact that in 1915 only fifteen counties in the United States were served by organized local health departments, whereas in 1942, 1,828 of the 3,070 counties were so served. For those not aware of the usual activities in a public health program, the chapter on this subject will be very enlightening and should serve as an excellent introduction to further reading.

The last chapter is a brief one relating to a "summary of trends and a consideration of certain needs." This is a well-written, authoritative, critical review of government in public health. It is highly recommended to anyone interested in health, either officially or unofficially. Each chapter is replete with references and documentation of statements made by the author. Several historical documents are reproduced, and there is a satisfactory index.

E. G. C.



**American Medical Practice in the Perspectives of a Century.** Bernhard J. Stern, Ph.D., New York, 1945, The Commonwealth Fund, 172 pages. Price \$1.50.

This is the first of a series of studies undertaken by the Committee on Medicine and the Changing Order of the New York Academy of Medicine to review the problems which now confront the medical profession and to serve as a background to assist in their solution. The author of this document is a lecturer in Sociology at Columbia University and visiting Professor of Sociology at Yale. He has had wide experience, has given much thought to sociology and medical progress, and has written frequently about both subjects.

At the outset the author presents data which demonstrates how the United States changed from an agricultural to an industrial economy and from a rural to an urban society and shows that these changes have "embraced all aspects of human relationships."

In the succeeding six chapters the author freely uses information he himself has gathered, information from the National Health Survey, reports of the Committee on the Cost of Medical Care, U. S. Public Health Service reports, and reports of the National Resources Committee to review again the subjects that are being put before us both in medical and lay journals from time to time—the expanding horizons of medicine, the specialist and the general practitioner, the supply and distribution of physicians, the patient load in medical practice, the income of physicians, and the distribution of medical services.

The book presents a brief summary of these points, and there is a list of some 200 references for those who would search for additional information. Just how valuable a contribution this document proves to be will depend upon how widely the book is read. This reviewer suspects the distribution will be primarily among those who have already informed themselves about these matters. Those who have not will probably continue to get their information by hearsay.

The book is recommended for those who wish to inform themselves by means of a brief review of these subjects, and who would like to be provided with a good list of references for further reading.

E. G. C.

**A Future for Preventive Medicine.** Edward J. Stieglitz, M.D., F.A.C.P., New York, 1945, The Commonwealth Fund, 73 pages. Price \$1.00.

There are many who will agree with the author's statement that "the recent approaches to preventive medicine can be divided into two major fields: (1) control of the environment to render it relatively innocuous, and (2) the improvement of the resistance of individuals who may be exposed to deleterious environmental influences." However, there is another major field in the approach to preventive medicine which many observers will add, and indeed one which is discussed in one form or another by the author throughout the book; detection of disease process early enough for interruption in favor of the individual.

The outstanding theme of the book throughout its sixty-eight pages is that health is a privilege and not a right; that it cannot be given to an individual by medical science or by government, but that it must be earned through the efforts of the individuals themselves with the assistance of those who are competent to help, the physicians themselves.

Much has been accomplished over the years in the prevention of illness by control of environment, but "modern sanitary facilities have been popular because they offered convenience and physical comfort, not because they offered greater safety to health." Until the attitude that health is an inalienable right is abandoned; so long as every illness is considered an intrusion beyond the control of the individual; and until attention is focused upon men, women, and children, who may become ill, rather than upon disease, very little will be accomplished in constructive health.

After a discussion of the accomplishments of preventive and curative medicine in a chapter entitled, "Health Over the Last Forty Years," in terms of the changes in the age structure of the population, changes in mortality, and changes in morbidity, the author presents a program of preventive medicine. Although he points out that in the selection of

the title, "A Future for Preventive Medicine," he deliberately chose the indefinite article "a" rather than the definite article "the" because there are other possible futures, it is evident that he feels strongly that the program presented is the most logical and fruitful approach to preventive medicine in the future. He makes a strong case for his ideas, and although there are many who will not agree with everything that is said, everyone will be stimulated by his provocative statements.

In addition to a plea for the continuance of public health activities which have to do primarily with mass measures to minimize health hazards, he insists that private health efforts concerned directly with the individual must be given greater attention than ever before. There must be research and education. "Physicians everywhere must cease shirking their educational responsibilities."

Other physicians can follow the lead of pediatricians in constructive medicine. "Well Adult Clinics," with individualized constructive medicine for adults, should be possible if the population can be shown that the maintenance of health is its own responsibility. The economic difficulties engendered by such a plan are dismissed in too few words.

According to Dr. Stieglitz, the measurement of health, although difficult, expensive, and time-consuming, is the foundation of personal preventive medicine. This is accomplished by the "periodic health inventory" (rather than the term periodic examination), the objectives being (1) the evaluation of health by diagnostic study, which should include measurement of reserve capacity, (2) early detection of insidious disorders in their incipency, (3) detection and correction of minor but potentially detrimental defects, (4) analysis of habits of living, and (5) direct personalized health education.

This is a very interesting and enlightening book, written by a man who has given considerable thought to the matter. The concept of preventive medicine presented is the modern one and corresponds closely with the ideas of many interested in this particular field. The book is recommended very highly for physicians and medical students. There is an excellent list of sixty-seven references.

E. G. C.

**Medical Education and the Changing Order.** Raymond B. Allen, M.D., Ph.D., New York. 1946, The Commonwealth Fund, 142 pages. Price \$1.50.

This monograph, by the dean of the College of Medicine of the University of Illinois and president-elect of the University of Washington, is one of the series being issued under the auspices of the Committee on Medicine and the Changing Order of the New York Academy of Medicine. As an exposition of the philosophy of one of the more thoughtful leaders in medical education, it deserves a careful reading by everyone interested in medical education and practice. Regardless of whatever changes may evolve in the social and economic phases of the practice of medicine, medical care in the final analysis depends upon the character and quality of medical education. This basic truth has been all too frequently disregarded in the rather hectic discussions of medical organization and economics which have been taking place in recent years.

Dean Allen's underlying theme is that medical education in its development and changes has reflected in large part the social, industrial, and cultural status of the particular period. He says that in the present period, technological progress has outpassed social development in all phases of living, and medical education and practice must meet the changing order. He is not pessimistic, but realizes the challenge of the times.

"Tomorrow's world has the power and resources to meet man's every need. Whether man has the wisdom, humility, and social consciousness to use his new-found powers for the constructive purposes of all mankind is the most important question of our times. The free men of democracy have proved that democracy has the inherent strength to be victorious in a world at war; they have yet to prove that they can win a durable peace. Never before has the spiritual and moral life of man faced a test of this portent for good or evil." (p. 136.)

Turning to the more direct matter of medical education, the author finds that it has been so occupied with the tremendous technological advances of the last few decades that it has neglected to prepare the doctor to fill a broader role as a responsible leader in the

community. This implies a thorough understanding of "the social, industrial, and economic patterns of which he is a part." Preventive medicine should be increasingly stressed in the education of the physician, not simply specific preventive technique and public health, but the "basic environmental conditions in the home, school, factory, and office which make for healthful living or its opposite."

The author suggests no specific changes in the practice of medicine as a cure for the unequal distribution of medical care and the economic problems of the cost of adequate medical care for all. His own viewpoint toward these matters can be summed up by another quotation:

"Physicians of the future must be capable of taking their places as responsible leaders in the community and of viewing the problems of medical service dispassionately. Unless they recognize the right of every person to adequate medical service, the medical profession will degenerate to the level of a trade in which, as tradesmen, physicians will be concerned merely with the technique of their trade. The medical profession cannot assume full responsibility for supplying complete medical service everywhere; it is no more responsible for the inadequacy of medical service in certain economically depressed regions of the country than teachers are responsible for the high illiteracy rates which are often found in the same places. It is under obligation, however, to cooperate fully with voluntary and public agencies so that together they may create the economic and social conditions which make possible an adequate medical service for all."

More specific ideas as to medical education, which, in a sense, are an appendage to the author's philosophy of education in general and the role of the physician, are as follows: (1) He looks for a better, more cultured type of medical student—an expression undoubtedly of his experience as a dean. (2) He feels that teaching ability should have more recognition in the selection of the medical faculty—an opinion held by many medical students. (3) He raises the question as to the sharp departmental lines under which nearly all of our medical school faculties are organized, and as to whether this is consistent with "the trend toward unity which is developing within the medical sciences themselves." (4) He urges that the faculties of our medical schools accept their responsibilities at the faculty rather than the departmental level. These are only a few of the points and suggestions expressed by the author.

It is a most thought-producing monograph, which unquestionably will not only influence medical education but medical practice. Throughout all, the importance of the human relationships of medicine is stressed as contrasted with its technology. This humanistic attitude is well summed up in the closing sentence of the book, "It takes a man, not a machine, to understand mankind."

B. S. V.

**Atlas of Blood in Children.** Kenneth D. Blackfan, M.D., and Louis K. Diamond, M.D. Illustrations by C. Merrill Leister, M.D., New York, 1944, The Commonwealth Fund. Price \$12.00.

There have been numerous books on hematology published in the past few years, but few have been devoted to infants and children exclusively. This book fulfils this need and is an important contribution to the pediatrician, general practitioner, and hematologist.

The outstanding feature of the book is the seventy brilliantly executed plates in eight colors from selected fields of blood films stained by Wright's method. The illustrations were done by Doctor Merrill Leister and not only reflect an outstanding artistic ability but are faithful reproductions of what he actually observed under the microscope. This is attested by the plates on leucemic cells which were apparently made from faded slides but are represented just as they were observed. If the atlas is reprinted, these plates should be replaced by illustrations of cells with their normal nuclear pattern and not that due to fading. This is a minor defect and does not mar the otherwise excellent work of this section. Opposite each plate is a line drawing, diagrammatic key permitting the reader to quickly identify the colored representation of the cells. The first few illustrations portray

the developmental cycle of cells of the erythroid, myeloid, lymphoid, monocyte, and thrombocyte series. Then follow patterns of the blood films in normal children at various age periods. The rest of the illustrations are devoted to depicting representative fields of blood films of various pathologic states involving the erythroid and leucopoietic tissues.

Besides this excellent atlas feature which more than justifies the cost of the book, there is a text of 144 pages and a comprehensive bibliography of thirteen pages arranged according to diseases. The text material, although concise, is practical, current, and authoritative. Each disease is briefly discussed from the standpoint of etiology, symptoms, laboratory data, diagnosis, prognosis, and treatment. Occasionally case records are introduced to crystallize the descriptive material. The introductory chapter on the origin and development of blood cells adheres religiously to the polyphyletic theory of Sabin and Doan. However, this material does not blend with the author's use of the neounitarian term "stem cell" to describe those immature cells found in acute leucemias which cannot be positively identified as a myeloblast or lymphoblast. Further, one may question the use of the terminology of "megaloblast" to describe the earliest precursor of the normal red cell series. If the cells pictured on plate 1 are the author's idea of megaloblasts then it is a matter of misuse of the term, for the cells illustrated on plate 1 are unmistakably erythroblasts. The discovery of folic acid and its specific effects in folic acid deficiency anemias in children makes positive identification of megaloblasts of more than academic interest. This should receive consideration in the next reprinting of the atlas, for the book is very outstanding in other respects.

Despite these minor criticisms one can recommend this book as a scholarly contribution to the pediatrician and hematologist. The Commonwealth Fund is deserving of commendation for subsidizing the cost of publication so that it could be made available to the reader at such a low cost. The atlas will undoubtedly be oversubscribed and it is hoped that the authors will make the indicated changes in the second printing.

H. G. P.

**Hematology for Students and Practitioners.** Willis M. Fowler, A.B., M.D., New York and London, 1945, Paul B. Hoeber, Inc., 449 pages. Price \$8.00.

This book on hematology corresponds precisely to its title. It was not written from the viewpoint of academic hematology but from the point of view of an internist interested in presenting as simply and as clearly as possible the practical aspects of the subject. The organization of the text is traditional except for an excellent chapter on transfusion of whole blood and blood derivatives which was written by Dr. Elmer DeGowin. This part of the book is current, comprehensive, and reflects the author's rich background in the subject. It is the feature of the book. The chapter on deficiency anemias is also well done and is a field wherein Doctor Fowler is particularly well qualified to write because of his extensive clinical and experimental work.

The other chapters are well written but are not as current or original in their style of presentation. Some of the information on the so-called "Banti's syndrome," Cooley's anemia, agranulocytosis, Lederer's anemia, and macrocytic anemia are somewhat outdated by reports in current medical literature. The introductory chapters on the hematopoietic system, erythrocytes, leucocytes, thrombocytes and normal hematologic values are concise, clearly presented, and adequate for the readers they were intended to reach. The concluding chapter on hematologic methods is also well organized and sufficient in essential detail for a book of this type.

The bibliography is well selected and ample enough for the material in each chapter except that in some cases significant current references have not been included. The printing on high grade glossy paper is a feature one seldom finds in recent medical books. The illustrations, charts, and diagrams are generous and sharply reproduced in black and white and colors. The colored reproductions of blood cells on the whole are good and those that are not would offend only the hematologist. The microphotographs in black and white are sharp and faithfully portray what one sees in the microscope.

The chapter devoted to hematology in infancy and childhood is inadequate for those specializing in pediatrics and apparently was not intended to meet the needs of this group. The book will also not find much favor with the hematologist or clinical pathologist. Its simplicity of presentation is, however, ideally adapted for the average general practitioner and the medical student beginning his clinical study who desire general orientation in the field of hematology.

H. G. P.

**Quarterly Review of Pediatrics.** Irving J. Wolman, M.D., Editor-in-Chief, University of Pennsylvania School of Medicine, Vol. 1, No. 1, February, 1946, Washington, D. C.; published by Washington Institute of Medicine.

This is a new type of publication in the field of pediatric literature, similar to those in other fields of medicine by the same publishers which have been available for some time. It is made up of abstracts, summaries, and references to the important new articles selected from national, state, and special journals from this country and abroad, prepared by physicians and others familiar with the special subjects assigned to them. The abstracts are not original articles or reviews as the title might indicate though interpretative or critical comments are given by the editorial staff in judging the pertinence and value of the individual contributions.

Issues will appear quarterly, in February, May, August, and November. The first number includes 122 pages. The abstracts are grouped by subtitles with free cross-references and an index by both subjects and authors. The subject index is unusually well done, indicating all the key words in a title by many cross references. The individual abstracts include the full title of the original article, the author, and reference to the location of publication. Articles in foreign languages include the original language as well as the translation in the title. It is planned that the abstract will be a digest of the articles including especially all the original data. Many of the subsections have at the end a list of references to current articles on that subject. This will enable the reader to know of the articles which have appeared during the quarterly period even though such articles may not have been included as an abstract. Many of the references, however, contain a brief statement of the substance of the article. Particular effort is made to indicate articles containing reviews of the literature on the special subject. The dates on the articles abstracted indicate that prompt publication of the abstract will keep the reader fresh and up to date. This is a most essential feature, for abstracts a year or more old are hardly more than a compilation. It requires a well-organized machinery to have abstracts published promptly and it will tax the quality of the editors and publishers to meet this requirement. The "Bookshelf" or book review department shows a broad coverage of subjects. The reviews are brief and informative rather than critical.

The form of the publication is of high quality. The paper is soft and durable and takes print clearly; the type is well arranged and makes for easy reading. The titles cross the page but the abstract is in double column—again easy reading.

The publishers have chosen a versatile and experienced editorial board with a wide range of interest in all branches of pediatrics. This is a high qualification to meet since pediatrics is a horizontal as well as a vertical specialty which dips into many other fields and specialized areas.

The Quarterly Review of Pediatrics should find an immediate, favorable reception for it fulfills a real need, and it is obvious that the need will be met adequately. It may be pointed out that everyone will find the Review necessary, especially the busy practicing physician. It is a publication to be kept close at hand for quick and frequent reference and will save many a "trip to the library" to dig out a wanted piece of information or "that article I cannot remember exactly."

H. McC.

**Pediatric X-ray Diagnosis.** John Caffey, A.B., M.D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, New York. Cloth, 711 illustrations. Chicago, 1945, Year Book Publishers, Inc., 838 pages. Price \$12.50.

This is a highly specialized book about a subject of great pediatric interest and importance. All too often the physician sends the patient to the roentgenologist for study and accepts the latter's interpretation of findings. This implies, among other things, that the physician's knowledge of the situation is not adequately correlated with the x-ray examination and that the x-ray findings are not utilized fully or to the best advantage. The physician must be informed roentgenologically and the roentgenologist must be informed clinically.

The author of the book, by his training, practice, and teaching in the studio, laboratory, clinic, and ward, has emphasized the real necessity of teamwork in roentgenologic studies. His compilation of such a text is the result of this training and has been awaited for a long time. The realization is fully gratifying. This reviewer has examined the book with an inquiring curiosity for errors of omission and commission which search has been fully disappointing. On the other hand, the commendable features are really stimulating.

The paper is of high quality to take the roentgen films fully reproduced. There are full illustrations and diagnoses and the text is brief, concise, well arranged in relation to the illustrations, and fully comprehensive. Both author and publisher may be congratulated on this technical perfection.

The book will be useful to many specialized professional groups, to clinical practitioners, and to the pediatrician. It is a *sine qua non* for everyday work. It should be on the daily "tool" shelf for constant reference and instruction.

H. McC.

**Nutrition and Chemical Growth in Childhood. Volume II, Original Data.** Icie G. Macy, Ph.D., Sc.D., Director of the Research Laboratory, Children's Fund of Michigan; with foreword by Laurence Reynolds, M.D., and a supplement by Julia Outhouse Holmes, Ph.D., Springfield, Ill., 1946, Charles C. Thomas, Pages xxv-xlii, 433-1460; Tables 123-597, Figs. 67-773, Cumulative index to Volumes I and II. Price \$10.00.

Volume I of this series was published in 1942. It tells of the long-term metabolic studies the author and her colleagues have conducted relating to normal children. As originally planned, Volume II was to deal with the interpretation of the metabolic data. Instead, the current volume is limited in scope to the presentation of the records of thirty-three children who have served as subjects for the studies. A third volume, not yet published, will deal with the analysis and interpretation of the data.

More than one-half of the children were studied recurrently for periods of many months. The records portray the progress of such children, each as a psychobiologic unit, and present in detail the static and progressive values for many physical and physiological constants. The book is profusely illustrated, principally with serial roentgenograms of specific bones and joints. One is impressed by the extensiveness of scope of the observations and the wealth of data relating to each child.

As a book of reference, this volume should serve a useful purpose in many fields of child development. In this regard, it deserves consideration apart from the series as a whole. The value of the data will be enhanced when interpretations are presented in the forthcoming Volume III of the series.

J. D. B.

**Diseases of the Nervous System in Infancy, Childhood and Adolescence.** Second Edition. Frank R. Ford, M.D., Associate Professor of Neurology, The Johns Hopkins University. Springfield, Ill., 1944, Charles C. Thomas, 1143 pages; 2221 bibliographical references; 164 illustrations; 22 charts; 14 tables. Price \$12.50.

The first edition of this book is dated 1937. The second is 1944. Its appearance, however, has been delayed to this date. There are 200 more pages, 468 new bibliographical

references, 40 new illustrations, and 11 new charts in this edition. The book has been rewritten wherever new material could be added or the old improved. The type face is somewhat larger, the page is about the same size, and the paper lighter. The actual amount of new material is considerably increased.

This book is reviewed in its second edition because of its essential usefulness to the pediatrician and its unique position in this field. The first edition has always occupied an "easy-to-reach" position on this reviewer's bookshelf. As stated in the preface, the author gives his own opinion on most subjects, but where his experience has been limited, he gives the general consensus among leading authorities. It, therefore, carries a personal touch throughout, which increases the interest on the part of the reader. The personal side of the author, however, broadens out to a base which includes many other workers and sources of material at the Johns Hopkins Hospital and Harriet Lane Home. The book can be recommended fully.

H. McC.

**Essentials of Pediatrics.** Fourth Edition. Philip C. Jeans, A.B., M.D., State University of Iowa; Winifred Rand, A.B., R.N., formerly Merrill-Palmer School, Detroit; and Florence G. Blake, R.N., M.A., Yale University School of Nursing. Philadelphia, 1946, J. B. Lippincott Company. 627 pages; 86 illustrations; 9 subjects in color. Price \$3.50.

This edition has been revised extensively by rewriting most of the material, and by the addition of new chapters on diseases of the eye, of the blood, and of the glands of internal secretion. The text matter has been reset in double columns with functional running heads. There is still no bibliography. The previous edition is six years old.

Problems of the well-baby clinic are presented concisely in a new chapter, "The Child Health Conference as a Means of Guidance" prepared by Martha B. Webb, R.N., of the Johns Hopkins School of Nursing. A new co-author, Miss Florence G. Blake, has directed the preparation of the material on nursing care.

The pediatrician will find this book useful in his daily work, for there is much in the nursing care that needs his information and attention. For those engaged in teaching, especially for those associated with schools of nursing or who are in charge of nursing services, the new edition will be most welcome. Maybe the next edition will include more in the field of public health nursing service. To nurses, practitioners, and pediatricians alike, this book can be recommended. It should serve as a strengthening bond between the several groups.

H. McC.

**Skin Diseases in Children.** Second Edition. George M. MacKee, M.D., Professor of Clinical Dermatology and Syphilology, Columbia University, and Anthony C. Cipollaro, M.D., Associate in Dermatology and Syphilology, Columbia University, New York. New York, 1946, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 448 pages; 225 illustrations. Price \$7.50.

This greatly enlarged and rewritten edition with 100 more pages appears after ten years. The first edition has been reprinted in England and a Spanish translation appeared in 1940. New chapters on diseases, important in childhood have been contributed by Dr. Eugene Traub on congenital anomalies, by Dr. Herman Beerman on syphilitic infections, by Dr. Frances Pascher on allergic dermatoses, and by Dr. Nathan Sobel on contagious diseases.

This edition is greatly improved, is rearranged extensively, and includes much new material especially in the field of treatment. This last point is natural since great changes have taken place with the introduction of new chemical therapeutic agents in the past decade. The book is another "must" for every pediatrician and general practitioner. The high standards of printing set in the first edition are preserved.

H. McC.

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## Original Communications

### INFANTILE CORTICAL HYPEROSTOSES

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**D**URING the spring of 1938 we studied an infant whose principal lesions were scattered swellings deep in the soft tissues and scattered cortical thickenings in several bones. After an extensive investigation no cause for the changes was found, and it was evident that this patient suffered from none of the recognized conditions in which cortical thickenings had been found previously, such as scurvy, rickets, syphilis, bacterial osteitis, neoplastic disease, or traumatic injury. In a specimen of the clavicle, simple hyperplasia of the cortex was demonstrated microscopically and there were no signs of an inflammatory cellular reaction or of subperiosteal hemorrhage. This patient was described in a discussion of the nonspecificity of cortical thickenings as related to the diagnosis of infantile skeletal syphilis in 1939.<sup>1</sup>

Three similar cases were encountered during 1939, 1940, and 1944. The group of four cases was reported as a new infantile syndrome under the title "Infantile Cortical Hyperostoses" in 1945.<sup>2</sup> In this paper we pointed out that a group of infants with similar manifestations had been recognized independently during the same period by Dr. Francis Scott Smyth at the University of California Hospital in San Francisco. The California cases have now been reported under the title "Periosteal Reaction, Fever and Irritability in Young Infants: A New Syndrome?"<sup>3</sup>

The three findings common to all of our patients were: (1) tender swellings deep in the soft tissues; (2) cortical thickenings in the skeleton; and (3) onset during the first three months of life. In all specimens of the skeletal lesions the findings were similar, cortical hyperplasia under a proliferating periosteum. Several bones were affected in each patient, but the distribution varied in different patients. Hyperostosis was demonstrated roentgenographically in the mandible, clavicles, scapulas, ribs, and the tubular bones of the extremities. All of the soft tissue swellings were deep and firm; none showed pitting on pressure, none were overly warm or discolored. Regional lymph nodes were not enlarged. The distribution of the soft tissue swellings was roughly the

From the Pediatric Department, College of Physicians and Surgeons, Columbia University, and the Babies Hospital.



same as that of the cortical hyperostoses, but small hyperostoses were visualized roentgenographically in several sites where soft tissue swellings had not been recognized clinically.

Other manifestations which were present in some patients but lacking in others were fever, pleurisy, anemia, and increase in the sedimentation rate of the erythrocytes. The course of the active disease was characteristically uneven. The fever was irregular. Soft tissue swellings appeared in one site when earlier swellings in another site were disappearing; also, the swellings recurred in the same site after partial or complete disappearance. All patients recovered after variable periods of many weeks or months. The cortical hyperostoses were visible roentgenographically months after the fever had subsided and after the soft tissue swellings had disappeared.

After prolonged investigation of four patients, the cause remained undetermined. Bacteriologic and serologic study of the patients and bacterial cultures of specimens removed from affected bones yielded no evidence of bacterial infection. Rickets and scurvy could be excluded on all counts. Traumatic injury was not observed in a single case either at home or in the hospital. Viral infection and allergy were considered as other possible causes but were not sufficiently investigated to either prove or disprove their causal significance.

This report contains data on six additional infants who show the characteristic findings of infantile cortical hyperostoses. Two of them were studied at the Babies Hospital. Four were recognized and investigated in other clinics by colleagues to whom I am deeply grateful for their interest and cooperation.

#### CASE REPORTS

**CASE 1.**—L. M., a white female, was first seen at the age of 6 months with the chief complaint of swelling of both cheeks for a period of five weeks. The mother was 39 years of age; she had eaten a normal diet and had been healthy during the pregnancy.

The patient was delivered after a normal gestation and was normal during the neonatal period. She thrived and developed normally on an evaporated milk formula; cereal, fruit, eggs, vegetables, and beef juice had been added to the diet at appropriate intervals. Vitamin D and orange juice were taken daily after the first week of life; for several weeks she had taken 3 ounces of orange juice daily. At 6 months she weighed 7.1 kg.

**Present Illness.**—At 4 months she began to be irritable at night; she awakened frequently and whined. At 4½ months her pharynx was said to have been inflamed and she had a fever; sulfonamide drugs were given for one week. Then swellings suddenly appeared on both sides of her face and the fever continued at a level of about 101° F. At the onset the swellings were tender and the patient drooled much saliva, especially at night. The sulfonamide therapy did not affect the swellings or the fever and after a few days she was admitted to a hospital for penicillin treatment. The latter had no beneficial effect on the swellings and the temperature remained above 101° F.

In the first examination at the Babies Hospital when she was 6 months of age, conspicuous facial swellings were still evident (Fig. 1A). They were firm and diffuse but not tender. The major portions of the swellings were located in the cheeks and submaxillary regions; the parotid regions were relatively free. The swellings were not fluctuant, were neither hot nor reddened, and regional lymph nodes were not enlarged. The buccal swellings protruded into the mouth and the oral mucous membrane overlying the internal swellings was normal. The openings of the parotid ducts were not visible. Motion of the mandible, both active and passive, was limited. Flexion of the head on the thorax was limited by the mandibular and cervical swellings. The clavicles were enlarged to palpation. No abnormalities

were detected in other parts of the body. On the day of admission the temperature fluctuated between 100 and 101° F. The tuberculin skin test was negative.

The hemoglobin was reduced to 8.6 Gm. per 100 c.c. (59 per cent); the red cells were reduced to 2.9 million per cubic millimeter. There were 13,000 leucocytes per cubic millimeter; 60 per cent polymorphonuclears, 25 per cent lymphocytes, 12 per cent monocytes, and 3 per cent eosinophiles. Kline's test on the serum gave a non-syphilitic reaction. There were no cold agglutinins in the blood. Sedimentation rate of the red cells was 142 mm. at the end of one hour. The Rh factor was pre-sent and the blood group was A. Agglutination tests on the serum were negative for the following organisms: *Eberthella typhosa* II and O; *Shigella dysenteriae* Flexner (group), *Shigella sonnei*, *Salmonella paratyphi* B, *Salmonella enteritidis*, *Salmonella choleraesuis*, and *Salmonella typhimurium*; *Brucella abortus*.



Fig. 1A.—Case 1. Facial swellings one month after their appearance.

The serum phosphorus was 6.8 mg. per 100 c.c., the serum calcium was not obtained; there were 15.0 units (Bodansky) of phosphatase per 100 c.c. of blood serum.

Roentgenograms of the entire skeleton disclosed scattered cortical thickenings in the following bones (Fig. 1B); mandible, both clavicles, and both ulnas. Later a small thickening appeared in the cortex of the right radius. The ribs were not affected and there was no evidence of pleural exudate as in three of the earlier patients.<sup>2</sup>

A block of bone was removed from the thickened right clavicle. At the operation the periosteum was swollen markedly. The microscopic section showed hyperplasia of the cortex under an actively proliferating periosteum; there were, however, no signs of inflammation or subperiosteal bleeding. Aerobic and anaerobic cultures from the right clavicle yielded no bacteria. Virus studies on the same material have not been concluded.

During the first week of hospital residence a mild fever was present; the maximal daily temperature varied between 100 and 101.5° F. During the second and third weeks there was no fever. The swellings in the face began to diminish during the second hospital week.

The infant was normally active and happy in the hospital. At the end of three weeks the facial swellings were small but still visible; they disappeared completely later at home. Her family physician reports that she has remained asymptomatic without recurrence of the facial swellings during eight months at home.

The mandibular findings in the roentgenogram (Fig. 1C) changed very little with the passing of time in contrast to the rapid fluctuations of the clavicular and ulnar thickenings (Fig. 1D).

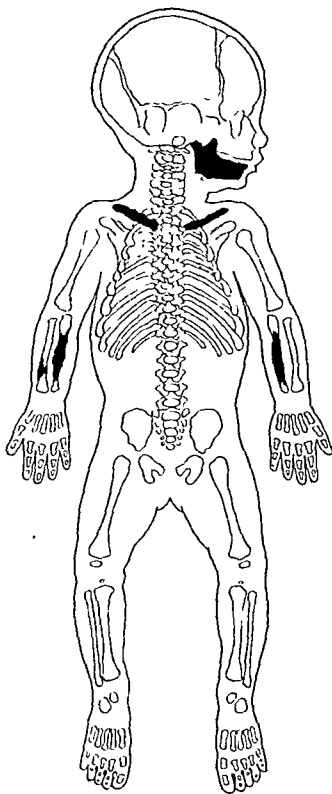


Fig. 1B.—Case 1. Diagram of the skeleton showing the scattered cortical thickenings in the mandible, both clavicles, both ulnas, and the right radius.

CASE 2.—A. M., a white female, was first seen when she was 27 months of age with the complaint of pain in the legs which had been present for seven months. She was normal at birth and thrived during the first year on a normal diet. She had had an adequate amount of Vitamin C which had been taken daily since the early weeks of life; Vitamin D had also been taken regularly in adequate amounts.

She had no complaints until the eighteenth month when she became “fussy” and lost her appetite. Hyperirritability and anorexia persisted until the twentieth month when tender hard swellings appeared over the left tibia and in the dorsum of the left foot. There was no redness in the swellings but the overlying skin was shiny. After a few days the swellings became so large and tender that she could not walk or wear shoes. After the first week the swellings diminished somewhat in size and the tenderness was not so marked; her appetite improved at the same time. During the twenty-third month excessive sweating at

night was observed at home and casts and albumin were found in the urine. Urethrotigonitis was diagnosed after cystoscopic examination. During the twenty-sixth month anorexia became more marked and the left leg became swollen, tender, and shiny for a second time.



Fig. 1C.—Case 1. Roentgenogram of the mandible in left lateral oblique projection showing swelling, cortical thickening, and sclerosis of the left side of the mandible.



Fig. 1D.—Case 1. Rapid, progressive sclerosis of the right clavicle. 1, Five weeks after onset the clavicle is partially covered by a shadow which approximates water density. 2, Six weeks after onset, the clavicle is now completely enveloped in a heavy bony shell of calcium density. One month later, in a film not shown here, the cortical thickening was reduced to paper thinness.

Fever had never been observed and there were no facial swellings as in Case 1. At twenty-seven months the only significant finding in the physical examination was a firm swelling of the left leg below the knee with tenderness of the left tibia. The swelling extended into the

dorsum of the foot; there was no hyperemia or edema. The temperature was 100° F. the first day and 100.5° F. the second day, but it remained below 100° during the remainder of a hospital residence of twenty days.

The red blood cells were normal in number and contained a normal amount of hemoglobin. There were 12,000 leucocytes per cubic millimeter; 59 per cent polymorphonuclears, 39 per cent lymphocytes, and 2 per cent monocytes. The sedimentation rate of the erythrocytes was 22 mm. at the end of one hour. The urine was normal chemically and cytologically.

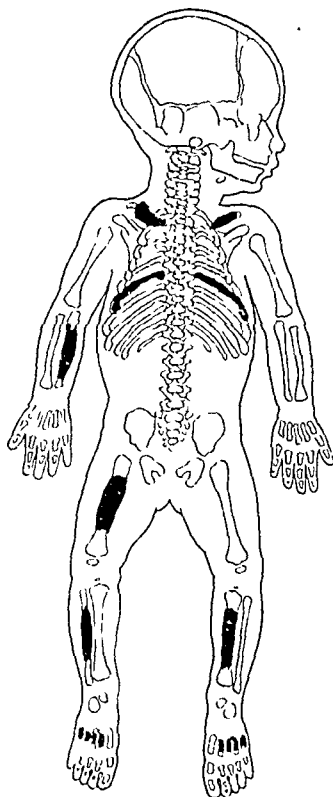


FIG. 2A.—Case 2. Diagram of the skeleton showing scattered hyperostoses in both clavicles, the right and left seventh ribs, right ulna, right femur, right fibula, left tibia, and several metatarsals in both feet. The mandible was not affected.

Phosphorus, calcium, and phosphatase were present in normal amounts in the blood serum. The blood proteins were present in normal amounts and in normal proportions. The prothrombin time was 20.3 seconds.

Culture of the blood yielded no growth and Kline's test gave a nonsyphilitic reaction. Agglutination tests for the following bacteria were negative; *Eberthella typhosa* H and O; *Shigella dysenteriae* Flexner (group), *Shigella sonnei*, *Salmonella paratyphi* B, *Salmonella enteritidis*, *Salmonella choleraesuis*, and *Salmonella typhimurium*; *Brucella abortus*.

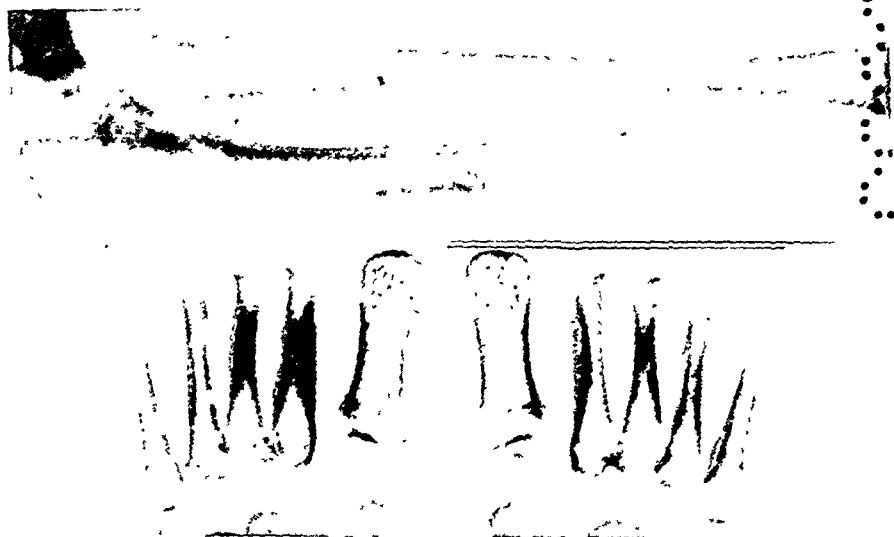
Kajdi's Vitamin C tolerance test gave an index of 6.0 which was interpreted to indicate a low reserve of Vitamin C.

Roentgenograms of the entire skeleton were made and cortical hyperostoses were found in both clavicles, the right and left seventh ribs, the right ulna, right femur, right fibula, left tibia and the metatarsals in both feet (Fig. 2A). The cortical thickenings in the left clavicle, the ulna, tibia and femur were all lamellated (Fig. 2B, I). Lamellation has not been found in the proved early stages of bone lesions in any patient and its presence probably indicates

a long-standing bone disease. The second, third, fourth, and fifth metatarsals in both feet were thickened; the first metatarsals in contrast were normal (Fig. 2B, 2).

The patient began to improve a few days after admission to the hospital. As the pain in her legs and feet diminished, she became more active. When she was discharged after twenty-two days, she was walking and eating normally. Roentgen examination at 29 months of age showed all the bone lesions to be still present and not significantly changed. The patient is now well at home and has been asymptomatic during one year since discharge from the hospital.

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Fig. 2B.—Case 2. 1, Lamellated thickening of the cortex of the right ulna. 2, Symmetrical cortical thickenings in the second, third, fourth, and fifth metatarsals of both feet. The first metatarsals, in contrast, are not involved. The phalanges were normal.

CASE 3.—W. O., a white male, was a patient of Dr. Richard Kegel of Cooperstown, N. Y., who kindly provided the clinical data and the roentgenograms for this report. The infant was born of a healthy mother after a normal gestation; the birth weight was 7 pounds. A cleft in the soft palate was identified during the neonatal period. Breast feeding was discontinued after two days and he was given a cow's milk formula with adequate Vitamin D and orange juice daily.

During the first six weeks he thrived; he had been taking 1 ounce of fresh orange juice and 4 drops of Navitol (Vitamin D) each day. When 6 weeks of age he was 23 inches in length and weighed 8 pounds, 4 ounces.

At 7 weeks, without premonitory symptoms, a large swelling suddenly appeared in the left cheek. Examination disclosed a poorly defined lump in the left cheek, most marked near the ramus and angle of the mandible. This mass did not seem to be painful or tender and was not discolored or excessively warm. The rectal temperature was 98.8° F. There were 21,000 leucocytes per cubic millimeter; 53 per cent polymorphonuclears, 42 per cent lymphocytes, 3 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. Roentgen examination of the mandible at this time showed a soft tissue swelling in the submaxillary region but the mandible itself was normal. Sulfadiazine was given for seven days without noticeable effect on the facial swelling.

At 9 weeks of age, two weeks after the onset, the facial swelling on the left side began to increase in size and a new swelling appeared suddenly in the right cheek. At this time there were 11,100 leucocytes per cubic millimeter; 46 per cent polymorphonuclears, 51 per cent



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Fig. 3A.—Case 3. 1, The left side of the mandible is normal roentgenographically, although a soft tissue swelling under the mandible was visible in the original film. 2, The same projection of the mandible at 11 weeks of age; cortical thickening on the underside of the mandible is now clearly visible (arrow). (Drawings of roentgenograms.)



Fig. 3B.—Case 3. Photograph of the facial swellings at 12 weeks of age, five weeks after the appearance of the swelling on the left side and three weeks after the appearance of the swelling on the right.

lymphocytes, and 3 per cent monocytes. At eleven weeks the right and left facial swellings were approximately the same size; roentgenograms at this time showed a distinct cortical thickening of the left side of the mandible (Fig. 3A). At twelve weeks the facial swellings were still conspicuous (Fig. 3B).

Despite the persistence of these swellings there were no associated constitutional or local symptoms and the infant continued to thrive. The patient remained afebrile. At the end of three months he weighed 11 pounds and was 25 inches in length. At 5 months he weighed 14 pounds.



Fig. 4A.—Case 4. Progressive changes in the left tibia and fibula from the third to the fourteenth week after onset. 1, Three weeks after onset the medial side of the tibia is covered with a faint, short, thin strip of water density (arrows). 2, Five weeks after onset the tibia and fibula are surrounded by long, thick, sclerotic envelopes of calcium density. 3, Eight weeks after onset the cortical thickenings have increased in depth and density. The medial surface of the hyperostosis is now rough. 4, Fourteen weeks after onset the hyperostoses are shrunken in comparison with earlier findings. The absence of metaphyseal and epiphyseal changes suggestive of scurvy at all stages is noteworthy. There is a striking absence of transverse lines in these last films.

At 4 months, films of the entire skeleton were made and no abnormalities were disclosed save for the mandibular thickening which now appeared lamellated. The entire skeleton was examined again roentgenographically at 9 months and appeared normal excepting the mandible. By this time the swelling on the right side of the face had disappeared and that on the left side was visible but much smaller than in the earlier examinations. Fever was not observed during these later months of observation.

CASE 4.—A. S. was a patient of Dr. Bruce Chown of Winnipeg, Canada, who kindly provided the clinical data and the roentgenograms for this report. She was born of a healthy mother after a normal gestation. During the first four months she grew and developed nor-



mally. Then, after a fretful night, her face was found to be swollen in the morning; there were no precursory symptoms. The next day her groin and legs were tender and her temperature ranged between 100 and 102° F. The fever and facial swelling persisted during the following three weeks when she was admitted to the Children's Hospital at Winnipeg.

On admission there she weighed 14 pounds and had a temperature of 101° F. The nutritional state was good but a moderate pallor was present. "The right side of the face was swollen from the ear forward to the maxillary prominence and from the temporal region downward to the inframandibular region." This swelling was firm; the skin overlying it was shiny but not discolored. The buccal mucosa internal to the swelling was normal. The right leg was diffusely swollen and shiny; the left leg was normal. Wassermann's test on the blood serum gave a nonsyphilitic reaction.



Fig. 4B.—Case 4. Massive symmetrical cortical hyperostosis of the ulnas eight weeks after onset. The radii in contrast are not affected.

Roentgenograms made at admission (three weeks after onset) showed indefinite thickenings of the shafts of the long bones which contained very little calcium (Fig. 4A). In later films (Figs. 4A and 4B), denser and thicker cortical thickenings appeared and then after a few weeks began to regress. Films were not made of the head or thorax so that the status of the mandible, the clavicles, and the ribs was never determined. In view of the fact that the mandibles were thickened in all other patients who exhibited facial swellings, it is probable that the mandible of this patient who had facial swellings was also thickened in the same fashion, although it was not demonstrated. The distribution of the hyperostoses in the extremities is shown in Fig. 4C.

In the hospital large doses of orange juice were given because of the possibility that the bone lesions were due to a deficiency of Vitamin C. During the first two weeks of this treatment there was some diminution in the size of the facial swellings but on the fifteenth day after admission (five weeks after onset) the swellings on the right side suddenly began to increase in size and at the same time a new swelling suddenly appeared in the left cheek. During the following seven days the swellings subsided but suddenly recurred again after three

weeks notwithstanding the daily intake of large amounts of orange juice. She remained in the hospital for seven additional weeks until sixteen weeks after the onset. A daily fever varying between 99 and 101° F. persisted until discharge from the hospital; otherwise she was without symptoms.

CASE 5.—P. F. was a patient of Dr. Clement Smith of Detroit to whom I am indebted for the clinical data and roentgenograms in this report. At 22 months of age this boy was admitted to the Children's Hospital of Michigan with the complaints of aching joints, refusal to walk, and recurrent fever of six weeks' duration. He was born after a normal gestation by spontaneous delivery; the mother's serologic tests for syphilis were negative during the pregnancy. The birth weight was 6 pounds. He was breast fed during the first six weeks and then given an evaporated milk formula. Cod-liver oil and orange juice were started a few days after birth. The orange juice was taken well; for several months prior to the onset of this illness 2 ounces of orange juice had been ingested daily.

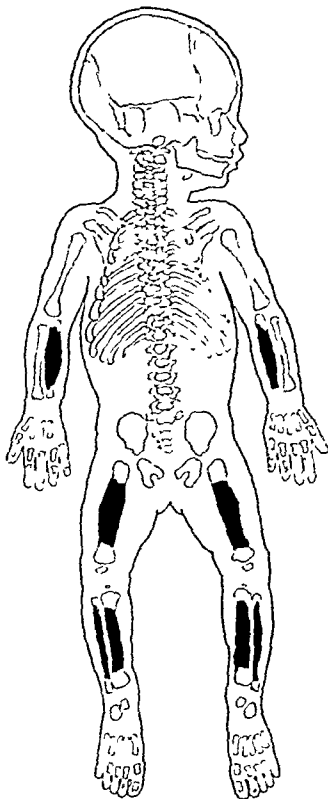


Fig. 4C.—Case 4 Diagram of the skeleton showing the distribution of the cortical hyperostoses in the extremities. The head and thorax were not examined roentgenographically and the status of the mandible, clavicles, scapulas, and ribs was not determined.

He was healthy until six weeks before admission, when he became listless and inactive if left alone but was hyperirritable and nervous when disturbed. The legs and arms were painful during movement and tender on manipulation; he cried when he was picked up. He seemed to be feverish at home, but the temperature was not measured. Rheumatic fever was suspected by his physician.

On admission he was found to be well nourished but very irritable. All of the long bones in the extremities were tender to pressure. Motion at the joints was free and no

periarticular swellings were observed. There were no facial swellings. No significant positive findings were revealed in the hospital other than the roentgen changes. The urine was normal microscopically and chemically. The hemoglobin measured 80 per cent; there were 14,000 leucocytes per cubic millimeter; polymorphonuclears 51 per cent; lymphocytes 49 per cent. The skin did not react to tuberculin, and Kahn's test on the blood gave a non-syphilitic reaction. There were 6.1 mg. of phosphorus per 100 c.c. of serum, and 10.7 mg. of calcium. The serum phosphatase equaled 10.7 Bodansky units per 100 c.c.

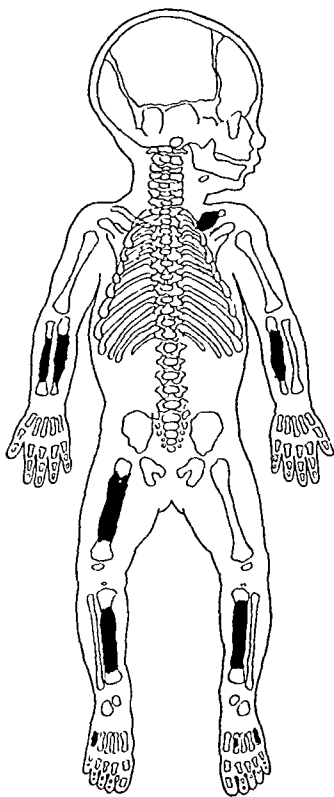


Fig. 5A.—Case 5. Diagram of the skeleton showing the distribution of cortical hyperostoses. The head was never examined roentgenographically.

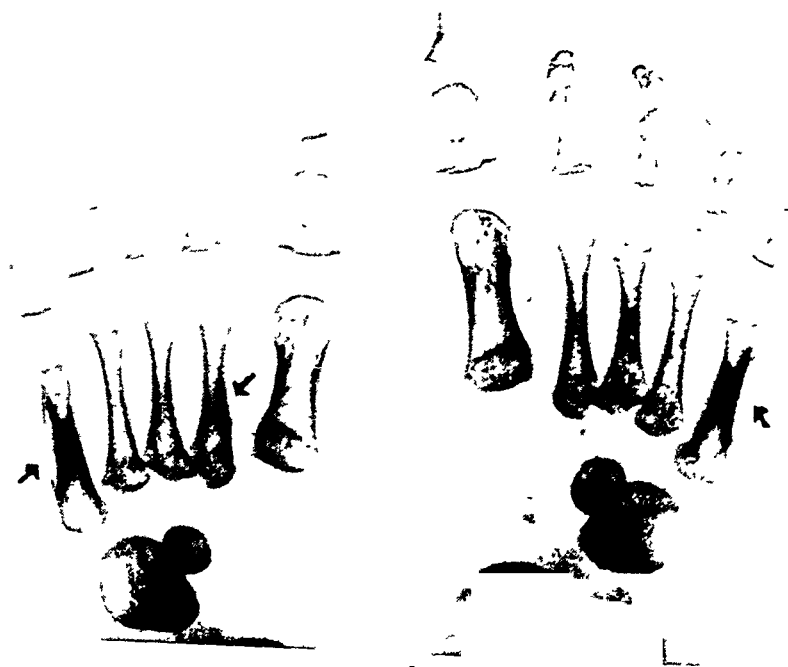
Roentgenograms of the thorax, pelvis, and extremities disclosed multiple cortical hyperostoses scattered in the left clavicle, both ulnas, left radius, right femur, both tibiae, and three metatarsals (Fig. 5A). The changes were pronounced in both ulnas (Fig. 5B, 1) and barely perceptible in the left radius and absent in the right radius. Both of the fifth metatarsals exhibited massive cortical thickenings (Fig. 5B, 2); the remainder of the metatarsals were unaffected save the second left metatarsal which showed slight thickening of the medial segment of its cortex. The phalanges were normal in the hands and the feet; the metacarpals were not involved. All of the affected bones were free of scorbutic changes in the metaphyses and in the epiphyseal ossification centers.

In a specimen of bone removed from the tibia, hyperplasia of the cortex under the periosteum was found; there was no inflammatory cellular infiltration and no evidence of subperiosteal hemorrhage.

During a residence of two weeks in the hospital the tenderness in the extremities gradually subsided and the patient was asymptomatic at the time of discharge.

CASE 6.—A. L., a white male 3 months of age, was admitted to the Charles V. Chapin Hospital in Providence, R. I. (data through the courtesy of Dr. Richard K. Whipple) with a chief complaint of swelling of the right side of the face for five days. Prior to the present illness, the infant had thrived since his birth on Jan. 25, 1946. The delivery was normal and

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Fig. 5B.—Case 5. 1. Long, thick hyperostosis in the left ulna. The ulnar side of the radius is also slightly thickened. 2. Symmetrical hyperostoses in the fifth metatarsals. There is also some cortical thickening on the medial side of the second left metatarsal.

the birth weight was 8 pounds. At the time of admission he was on a three hour feeding schedule which included the daily intake of 2 teaspoons of cereal, 1 ounce of orange juice and cod liver oil in unstated quantities. No allergic reactions had been noted; immunizing agents had not been administered. There were eight siblings in the family, all in good health.

The initial finding in this illness was detected nine days before admission when the mother noted that the right side of the face was tender. Three or four days later a swelling appeared in the site of the tenderness. The swelling gradually enlarged until admission. Food was taken by mouth without difficulty, but the infant vomited occasionally.



Fig. 64.—Case 6. 1, Cortical hyperostosis of the left parietal bone. Similar changes were demonstrated in the right parietal bone. 2, Thickening and sclerosis of the right side of the mandible five days after swelling was first detected in the soft tissues in the right side of the jaw. 3, Massive hyperostosis of the mandible twenty-seven days after 2.

At admission the only positive physical finding was the firm, tender swelling of the right side of the face and jaw which seemed to be attached to the mandible. Examination of the blood disclosed that hemoglobin was 68 per cent and that there were 4.7 million erythrocytes per cubic millimeter, and 24,000 leucocytes. The findings in the urine and spinal fluid were normal. The admission roentgenograms revealed thickenings and sclerosis of the right side of the mandible; the body, ramus, coronoid, and articular processes were all affected (Figs. 64, 2 and 3).

At the time of writing, the patient had been under observation in the hospital for five weeks. Fever was present on admission and has continued intermittently, reaching maximal levels of  $102.5^{\circ}$  F. The right-sided facial swelling became larger during the first hospital week; at the end of this first week a firm swelling appeared in the left side of the face. Two weeks after admission a swelling was noted in the scalp, on the right side; at the same time the conjunctiva and lids of the right eye became swollen. Then a swelling appeared in the scalp in the left posterior parietal region. Roentgenograms of the head showed symmetrical external thickenings of the parietal bones (Fig. 6A, 1). During the second and third hospital weeks, 2,700,000 units of penicillin were administered; during the fourth week he received 10 Gm. sulfadiazine. The fever and swellings were apparently not altered by either of these drugs. Five weeks after admission a swelling of the soft tissues was noted in the right sternoclavicular region and roentgenograms disclosed massive cortical thickening of the right clavicle. At the time of the last observation, hyperostoses had been demonstrated in both parietal bones, the mandible, and the right clavicle (Fig. 6B). No abnormalities were visualized in the ribs, scapulas, or bones of the extremities.

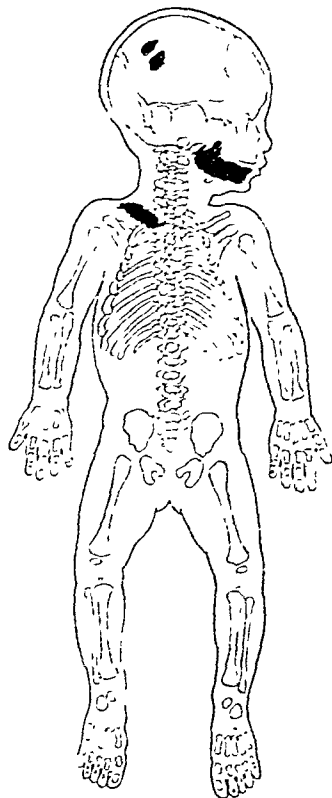


Fig. 6B.—Case 6. Diagram of the distribution of multiple hyperostoses in the right and left parietal bones, in the mandible, and in the right clavicle.

An anemia developed and was most marked in the third hospital week when the hemoglobin approximated 50 per cent and the erythrocytes numbered 3.9 million per cubic millimeter. A transfusion of 120 c.c. of blood was given. The number of leucocytes varied from 29,000 to 7,000 per cubic millimeter; the polymorphonuclears from 60 to 35 per cent, and the lymphocytes from 47 to 36 per cent. On two occasions the monocytes comprised 10 per cent of the total number of leucocytes. There was no eosinophilia. The Wassermann

and Hinton blood tests gave nonsyphilitic reactions. The tuberculin skin test was negative. Blood cultures were sterile. The concentration of calcium and phosphate in the blood serum was normal. Excretory urography was abandoned owing to positive cutaneous reactions to diodrast and skiadan.

#### COMMENT

The study of six additional cases supports the view that infantile cortical hyperostoses represent a disease which until recently has not been recognized as a clinical or roentgenographic or anatomic entity. The essential skeletal change has again been demonstrated to be subperiosteal cortical hyperostosis causing external thickening of the bone. The cause and pathogenesis of the disorder remain undetermined. Bacterial infections, scurvy, and rickets, trauma, and neoplastic disease all appear to be satisfactorily excluded as causal agents. Virus infection and allergic reactions have not been demonstrated or disproved.

As was to be expected, several new features were disclosed by the investigation of more patients; both the clinical and roentgen pictures are more variable than previously described. It is now evident that the onset may occur later than the third month of life; initial symptoms may appear during the second year (eighteenth month in Case 2 and twentieth month in Case 5). The duration of the active manifestations varied from eight weeks in Case 5 to nine months in Case 2. The uneven course of the disease was again well demonstrated in the recurrences and the remissions of the facial swellings in Case 4 and in the intermittent symptoms in Case 2.

In all cases the tender soft tissue swellings were deeply placed, showed no increase in local heat and were not visibly hyperemic. The subcutaneous fat overlying the swellings retained its normal radiolucency, the swellings appeared to be confined to the central shadow of the muscular masses which surround the bones of the extremities. It is noteworthy that facial swellings appeared in all patients with onset prior to the fifth month of life, but were present in neither of the patients with later ones (Cases 2 and 5). The scalp became swollen in Case 6, the first and only example of involvement of this part of the body. Later on, the conjunctiva and lids of this patient's right eye also became swollen. The nature of the soft tissue swellings and the tissue elements actually involved during the early phase of this disease are not known. In biopsies made several weeks after the onset of symptoms, Smyth and his co-workers<sup>3</sup> reported fibrosis, degeneration, and atrophy of the masseter muscle in one case, and degeneration with fatty and fibrous displacement of the intercostal muscles in another.

Five of our six patients exhibited fever. Fever in contrast was never detected in Case 3 although it was watched for carefully. The disease has now run its course in two patients without fever being recognized (see also Case 4 in reference 2). Two patients were moderately anemic, both had received sulfonamide therapy before the anemia was detected. In our first group of patients, two were anemic who had not received sulfonamides.

The most striking difference in the findings in our two groups was the absence of pleurisy in all of the six patients in the second group; in contrast,

three of the four infants in the first group showed roentgen signs of pleural exudate. It is to be remembered that pleurisy developed only in patients with extensive cortical thickenings in the ribs.

As in the first group, the number, distribution, and magnitude of the skeletal lesions varied greatly. The mandible alone was affected in Case 3. In contrast, neither facial swellings nor mandibular hyperostoses were observed in patients 2 and 5 who had the latest onsets during the second year. Mandibular and facial lesions were also absent in the two patients with late onsets described by Smyth and associates.<sup>3</sup> All of our patients who became ill prior to the sixth month have shown facial swellings (eight cases) and seven of these, all whose mandibles were examined roentgenographically, showed mandibular hyperostoses. This raises some doubt as to the validity of including the older patients in the same syndrome. We have included them because, save for the absence of mandibular involvement, they appear to be similar in all other important respects. Cortical thickenings of the metatarsals were demonstrated in both of the older patients, both of whom refused to walk at the onset of the disease. It is possible that trauma to the metatarsals incidental to walking and weight-bearing was partially responsible for the lesions in the metatarsals. The neighboring phalanges were not affected. We have not made roentgenograms of the feet in the younger infants; none of them have had swelling or tenderness of the feet. We have not demonstrated lesions in the hands in any patient.

The scapulas were not affected in any of these six patients. The ribs were thickened in only one infant (Case 2) and the costal changes were limited to the right and left seventh ribs. Clavicular hyperostosis was demonstrated in four cases, was absent in one (Case 3) and the clavicles were not examined roentgenographically in one (Case 4). The clavicles have been involved as frequently as the mandible, that is, in seven of nine patients who have had roentgenograms of the thorax. The ulnas appear to be considerably more vulnerable than the radii and may be markedly thickened when the radii appear to be normal (see Fig. 4B). We have not yet observed the converse. Fibular lesions may be present or absent when the tibias are affected, or fibular thickenings may develop in the absence of changes in the adjacent tibia. The bones of the calvarium have not been affected save in Case 6. I have, however, examined a patient in consultation, whose case is not reported here, who showed cortical thickenings in the edges of the frontal and parietal bones contiguous to the anterior fontanel in addition to thickenings of both clavicles and both ulnas.

Soft tissue swellings were evident clinically before cortical hyperostoses were visible roentgenographically in Cases 3 and 4. In the latter, tender swellings had been present in the leg for three weeks when the films showed no signs of excessive cortical bone in the tibia; two weeks later cortical thickening became visible and succeeding films showed an increase and then a regression of the tibial lesions. The lag in the appearance of the hyperostoses in roentgenograms must be taken into consideration in diagnosis. Successive films should be made for at least four weeks after the appearance of soft tissue swellings; absence of cortical hyperostoses during the first days after the onset is probably characteristic and is to be expected.



Although many and probably the principal clinical and roentgen features of this disorder have been revealed by the study of ten patients, many important questions remain unsolved. Observations at onset and during the early phases are unfortunately still meager. Biopsies of the soft tissue swellings and the skeletal lesions as well as bacterial and viral search during the first stage of the disease would probably throw much light on the cause and pathogenesis. Comprehensive investigation of allergic reactions early, near the onset, are essential before allergy can be evaluated properly as a causal agent. The favorable outcome in all cases has precluded necropsy.

In all patients the disease appears to have run its course unmodified by the therapeutic agents which have been used. Sulfonamides and penicillin have been equally ineffective in the few patients to whom they have been administered. Orange juice and ascorbic acid have failed conspicuously to cure or even prevent relapses. We plan to make the therapeutic trial with some of the new antiallergic drugs when the opportunity presents itself. There is no clinical evidence thus far that the disease is a contagious one; there have been no contact or sibling infections.

Infantile cortical hyperostoses can be readily confused with a number of conditions, especially if roentgenograms of the bones are not made or if they are made too early in the disease before the hyperostoses appear. The facial swellings have suggested the possibility of parotitis in some cases, as well as osteomyelitis of the mandible and neoplasm of the mandible. Swellings, tenderness, and painful pseudoparalysis of the extremities are all manifestations of scurvy. Fever, hyperirritability, and painful pseudoparalysis resemble some cases of poliomyelitis. Anemia, fever, and bone pain are a common complex of manifestations in many cases of infantile leucemia. Fever, pain, and tenderness in the extremities and increased sedimentation rate of the erythrocytes may point to rheumatoid arthritis or rheumatic fever; the latter was the admission diagnosis in Case 5. In active rheumatoid arthritis, regional cortical thickenings of the bones adjacent to the soft tissue swellings are not uncommon<sup>4</sup> and would be difficult to differentiate on roentgen grounds alone from the thickenings of the metatarsals demonstrated in Case 2. If and when satisfactory specimens of the soft tissue swellings become available, careful microscopic search should be made for tissue changes characteristic of the rheumatic and rheumatoid states.

#### SUMMARY

Six additional cases of infantile cortical hyperostoses are described. Ten cases have now been reported from this clinic. The findings indicate that this disorder is a new infantile syndrome for which the cause is unknown and the pathogenesis obscure.

The skeletal lesion is a hyperplasia of subperiosteal bone on the periphery of the cortex. Pleural exudate removed from one patient contained 500 monocytes per cubic millimeter. The nature of the soft tissue swellings and the tissue elements in them which are affected primarily have not been determined.

The components of the syndrome common to all patients are deep swellings of the soft tissues and cortical hyperostoses in the neighboring bones. Other important features lacking in some patients include fever, hyperirritability, pseudoparalysis, dysphagia, pleurisy, anemia, leucocytosis, monocytosis, increased rate of sedimentation of erythrocytes, and excessive serum phosphatase. Soft tissue swellings have been located in the scalp, face, neck, thorax, and extremities. Hyperostoses have been demonstrated in the calvarium, mandible, clavicles, scapulas, ribs and the tubular bones of the extremities including the metatarsals. The mandible and the clavicles are affected most frequently.

Initial symptoms have appeared as early as the third week of life and as late as the twentieth month. Duration of the active manifestations has varied from eight weeks to nine months. All patients have recovered. The course of the disease has not been modified by the administration of sulfonamides or penicillin.

#### REFERENCES

1. Caffey, J.: Syphilis of the Skeleton in Early Infancy; Nonspecificity of Many of the Roentgenographic Changes, *Am. J. Roentgenol.* 42: 637, 1939 (see Case 19, page 649).
2. Caffey, J., and Silverman, W. A.: Infantile Cortical Hyperostoses; Preliminary Report on a New Syndrome, *Am. J. Roentgenol.* 54: 1, 1945.
3. Smyth, F. S., Potter, A., and Silverman, W.: Periosteal Reaction, Fever and Irritability in Young Infants; a New Syndrome? *Am. J. Dis. Child.* 71: 333, 1946.
4. Caffey, J.: *Pediatric X-Ray Diagnosis*, Chicago, 1945, The Year Book Publishers, Inc., p. 774, Fig. 675.

## THE USE OF PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS IN CHILDREN

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EARLY reports on the use of penicillin in the treatment of subacute bacterial endocarditis have included histories of a small number of children. The outcome was favorable in every instance but one, in which the dosage employed was unusually small. Ten children less than 15 years of age whose endocarditis was caused by *Streptococcus viridans* have been described in sufficient detail in the literature to be included in this summary, and we have added four more whom we have observed.

Collins<sup>1</sup> treated a boy 10 years of age, who had congenital heart disease and bacterial endocarditis, with 1,400,000 units of penicillin administered intramuscularly over a period of fourteen days. The child recovered and remained well during a period of observation of six months. Among the twenty patients with subacute bacterial endocarditis treated by Dawson and Hunter,<sup>2</sup> one was a boy 13 years of age with an aortic and mitral valvulitis of rheumatic origin and a superimposed infection with *Str. viridans*. A total of 1,410,000 units of penicillin was administered by continuous intravenous drip over a period of twelve days together with heparin given by intramuscular injection. The blood stream became sterile and the patient remained well over a period of observation of six months. In a second report,<sup>3</sup> the same authors included the case of a 13-year-old girl with a congenital heart lesion, probably an interventricular septal defect, who developed a bacterial endocarditis due to one of the indifferent groups of streptococci. This patient was more refractory than their previous child and required a total of 34,400,000 units of penicillin before the symptoms subsided and the blood stream remained sterile. She recovered and remained well for a period of three months of observation. Since this infection was due to a streptococcus other than the *viridans* variety, the case history has not been included in the accompanying table (Table I).

Goerner and associates<sup>4</sup> reported the case of a boy 10 years of age who had a ventricular septal defect and bacterial endocarditis. This boy was one of the first patients treated with penicillin and he received only 240,000 units. He failed to recover. Two other children, 11 and 13 years of age, with the infection superimposed upon previous rheumatic infections, received much larger doses (9,120,000 and 4,900,000 units) and recovered. One was observed for twelve months and the other for six months and neither had further symptoms of the disease. The drug was administered by the continuous intravenous route and heparin was not used.

Among twenty patients reported by Flippin and associates<sup>5</sup> there were three children who were treated successfully. Their ages were 7, 10, and 12 years respectively. Two had congenital heart disease and the third had rheu-

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matic valvulitis. Each received 4,200,000 units administered by continuous intravenous drip over a period of fourteen days. No heparin was employed. They remained well for periods of observation ranging from thirteen to fifteen months.

Among the group of patients reported by Hirsh and Dowling<sup>2</sup> there was a girl 13 years of age with mitral and aortic valvulitis who had had symptoms of bacterial endocarditis for three months before treatment was started. She received 11,500,000 units of penicillin and recovered with no symptoms of the infection for a period of observation of four months.

Of special interest was the recovery of a child treated with penicillin administered orally. Burke and associates<sup>3</sup> observed a girl 11 years of age who had a ventricular septal defect and developed symptoms of subacute bacterial endocarditis four weeks before admission to the hospital. Blood cultures were positive for *Str. viridans* on three occasions. Penicillin was administered in doses of 100,000 units in double gelatin capsules every three hours. Two tablets of aluminum hydroxide were given from fifteen to thirty minutes before each dose. Blood levels of the drug varied from 0.078 to 1.24 units. A total of 11,200,000 units were administered during a fourteen-day period and the child recovered from the infection. She remained well for a four-month period of observation.

The four children of our series whose histories are reported here in detail had clinical evidence of subacute bacterial endocarditis and positive blood cultures for *Str. viridans*. Penicillin was administered by intermittent intramuscular injections, total dosage ranging from 6,000,000 to 8,500,000 units during periods of four to eight weeks. No heparin was employed. Recovery occurred in every instance and the patients have remained well for periods of one year or more.

#### CASE REPORTS

*Summary of Case 1.*—A white girl, 9 years of age, with a history of several attacks of rheumatic fever and a well-advanced mitral valvulitis suddenly developed acute symptoms of subacute bacterial endocarditis and embolism of an intracranial vessel. Treatment with 4,500,000 units over a period of eight weeks led to complete recovery from the bacterial endocarditis and the patient has remained well during a period of observation of eighteen months.

*CASE 1.*—This child had her first attack of rheumatic fever at the age of 5 years (1939). Several exacerbations of the disease occurred during the next two years and the cardiac signs at that time were suggestive of mitral stenosis. In the autumn of 1943 she was included in a group of children who received daily doses of 1.0 Gm. of sulfathiazole for the prevention of recurrences of rheumatic fever. She remained well throughout the year and in May, 1944, the treatment was discontinued.

Sept. 27, 1944, the child began to vomit, and a few hours later she became unconscious. No previous symptoms had been noted by the parents. When admitted to the hospital on September 28, she was still unconscious, had a fever of 102° F. and a few petechiae on the neck and in the sclera of one eye. The pulse was rapid, the heart enlarged, and there was a loud systolic murmur over the entire precordium. The spleen was large. The Kernig and Brudzinski signs were positive and the neck was rigid.

At this time the hemoglobin value was 14 Gm. per cent and there were 42,400 white cells per cubic millimeter, of which 92 per cent were polymorphonuclear leucocytes. The urine was negative. In cultures of the nose and throat secretions were hemolytic streptococcus and hemolytic *Staphylococcus aureus*. Blood cultures were sterile. The cerebrospinal fluid contained: 360 cells, the majority of which were polymorphonuclear leucocytes; 30 mg. per cent of protein; 694 mg. per cent of chlorides; and 54 mg. per cent of sugar. On the following day the cerebrospinal fluid contained 100 cells and the Pandy reaction was negative.

On the suspicion that the child had a meningococcemia with an early meningitis, sulfadiazine and penicillin were administered and during the next five days the patient improved rapidly and medication was discontinued.

On Oct. 15, 1944 (eighteen days after admission), the child's temperature rose to 103° F. and petechiae appeared on the cheeks and trunk. The spleen was large and tender. Sulfadiazine was administered once more, but the crops of petechiae continued to appear during the following few days. Four blood cultures taken on different days were all negative.

By November 1 (thirty-two days after admission), the child had improved considerably, but at this time a blood culture showed twenty-four colonies of *Str. viridans* per cubic centimeter. This organism was found to be sensitive to penicillin. Treatment consisted of the intramuscular injection of 10,000 units of penicillin every three hours for a period of twenty-five days when a total of 2,000,000 units had been administered. Sulfadiazine, which was administered simultaneously in oral doses of 10 grains every four hours, produced blood levels varying from 3.2 to 8.0 mg. per cent.

On December 2, a second course of 2,500,000 units of penicillin was instituted. Transfusions of whole blood were given on two occasions during the course of the illness.

All symptoms of acute illness had disappeared and seven consecutive blood cultures were negative within three weeks after intensive penicillin therapy had been started. The child was discharged Dec. 30, 1944, to a convalescent home where she has remained well for the period of observation of eighteen months.

*Summary of Case 2.*—A Negro boy, 12 years of age, with aortic insufficiency of rheumatic origin, developed mild symptoms of subacute bacterial endocarditis. Treatment with 6,800,000 units of penicillin over a period of thirty-eight days resulted in complete recovery from the bacterial infection and he has remained well for a period of observation of sixteen months.

*CASE 2.*—This boy had an attack of rheumatic fever at 10 years of age (1942). It is possible that he had had previous attacks, but the history was uncertain. A diagnosis of insufficiency of the aortic valve was made in 1942 and the child was referred to the Condon School for crippled children. On Nov. 11, 1944, while attending this school, he was included in the series of children who started taking sulfadiazine in doses of 7.5 grains daily as a measure to prevent recurrences of rheumatic fever. During the next few months, he developed no symptoms of rheumatic fever although he had several colds. On several occasions it was noticed that he was steadily losing weight, and by February, 1945, he had lost a total of 9 pounds. He had no fever during school hours and the routine urinalyses and leucocyte counts were normal. He gave a history of profuse sweating at night.

He was admitted to the hospital Feb. 12, 1945, for more complete study. For the first time, areas of tenderness were noted on the dorsum of the left foot and in the distal phalanx of the little finger of the right hand. The tenderness could be detected by pressure over the small bones rather than by motion of the joints. The spleen was palpable but not greatly enlarged. The heart was enlarged and a blowing diastolic murmur was prominent at the base. A soft systolic murmur also occurred at the apical area. The blood pressure was 130 systolic and 50 diastolic. Shortly after he was admitted to the hospital, he developed hemorrhagic areas in the sclera.

The laboratory tests included a leucocyte count of 5,000 per cubic millimeter, a hemoglobin value of 8.5 Gm. per cent and an erythrocytic sedimentation rate of 27 mm. per hour.

The Kahn reaction was negative. Roentgenograms of the chest demonstrated the enlargement of the heart with a maximum width of 12.5 cm. in a chest 22.5 cm. wide. Electrocardiograms demonstrated some abnormalities of shape of the S-T segments and depression of T waves in the second and third leads, findings often associated with myocardial damage.

The patient was treated with aspirin on admission because he seemed to have an exacerbation of rheumatic fever. However, four specimens of blood taken during the first week of his hospitalization all contained *Str. viridans* and penicillin therapy was instituted in dosage of 25,000 units administered intramuscularly every three hours.

He received a total of 6,800,000 units of penicillin during a period of thirty-eight days. Sulfadiazine in oral doses of 15 grains every four hours was likewise given. All symptoms promptly subsided and he began to gain weight. The hemoglobin content of his blood rose to 12 Gm. per cent and fourteen blood samples taken during the next two months were sterile. He has been observed frequently since his dismissal from the hospital sixteen months ago and has remained well.

*Summary of Case 3.*—A Negro girl, 8 years of age, with a congenital cardiac lesion believed to be a defect of the interventricular septum, developed mild symptoms of subacute bacterial endocarditis. She received 7,000,000 units of penicillin over a period of thirty-five days and made a complete recovery. She has remained well for a period of observation of fourteen months.

*CASE 3.*—This Negro girl was first seen in the cardiac clinic when she was 6 years of age (1943). At this time she had a rough systolic murmur at the left of the sternum in the third and fourth intercostal spaces. The heart was not enlarged and the electrocardiogram showed a P-R interval of 0.20 seconds. The spleen was not palpable. A Kahn test of the blood was questionably positive at this time, but was subsequently negative. No antisyphilitic treatment was given.

At a routine visit to the cardiac clinic on March 3, 1945, she had vague symptoms of abdominal pain. No tenderness or rigidity of the abdomen could be detected but the spleen and liver were both two fingerbreadths below the costal margin. Petechiae were observed on the left shoulder and on the thighs. The cardiac signs were the same as noted previously except that a short systolic thrill could now be detected at the left sternal border at the level of the fourth intercostal space. She had no fever or other symptoms. She was admitted to the hospital March 3, 1945, and initial blood culture, reported on March 8, contained *Str. viridans*. No other positive blood cultures were obtained, but this single positive culture together with the clinical signs of bacterial endocarditis seemed to warrant the immediate institution of therapy. Penicillin was administered every three hours in doses of 25,000 units intramuscularly for a period of thirty-five days until a total dosage of 7,000,000 units had been given. The dosage of sulfadiazine for the first four days was 7.5 grains every four hours and was reduced to 7.5 grains twice a day thereafter. The child made a complete recovery. No more petechia appeared and the spleen became smaller. Twelve blood cultures were negative.

Shortly after her discharge from the hospital on May 19, 1945, she developed fever and loss of appetite. The spleen could again be palpated about one fingerbreadth below the costal margin. Readmitted to the hospital, she improved rapidly. Repeated blood cultures were negative and no treatment was given. She has been observed frequently in clinic during the fifteen months since that time and has been entirely well, except for the original congenital cardiac lesion.

*Summary of Case 4.*—A white boy, 11 years of age, with mitral valvulitis of rheumatic origin, developed acute symptoms of subacute bacterial endocarditis. Following the administration of 8,500,000 units of penicillin, complete recovery took place. Four months later, when his tonsils and adenoids were

TABLE I. CHILDREN WITH SUBACUTE

AUTHOR	AGE (YR.)	SEX	CARDIAC LESION	DURATION OF SYMPTOMS OF ENDOCARDITIS BEFORE TREATMENT	TOTAL DOSAGE OF PENICILLIN
1. Collins <sup>1</sup>	10	M	Congenital	6 weeks	1,400,000
2. Dawson and Hunter <sup>2</sup>	13	M	Rheumatic; aortic and mitral valvulitis	3 months	1,410,000
3. Goerner and others <sup>4</sup>	10	F	Congenital; ventricular septal defect	1 month	240,000
4. Goerner and others <sup>1</sup>	13	F	Rheumatic; mitral valvulitis	5 months	9,120,000
5. Goerner and others <sup>4</sup>	11	F	Rheumatic; mitral valvulitis	6 weeks	5,200,000
6. Flippin and others <sup>5</sup>	10	F	Congenital	6 weeks	4,200,000
7. Flippin and others <sup>5</sup>	12	F	Rheumatic	16 weeks	4,200,000
8. Flippin and others <sup>5</sup>	7	M	Congenital	12 weeks	4,200,000
9. Hirsch and Dowling <sup>6</sup>	13	F	Rheumatic; mitral and aortic valvulitis	3 months	11,200,000
10. Burke and others <sup>7</sup>	11	F	Congenital; ventricular septal defect	4 weeks	11,200,000
1. Lyon	9	F	Rheumatic; mitral valvulitis	5 weeks	4,500,000
2. Lyon	12	M	Rheumatic; aortic valvulitis	3 months	6,800,000
3. Lyon	8	F	Congenital; ventricular septal defect	1 week	7,000,000
4. Lyon	11	M	Rheumatic; mitral valvulitis	3 weeks	8,560,000

removed, an additional 800,000 units of penicillin were given and no recurrence of the bacterial endocarditis took place. When observed a year after his initial attack of bacterial endocarditis, he was in good health.

CASE 4.—(This boy is a patient of Dr. Frank Seinsheimer and we are grateful for his permission to include this report.) In the Autumn of 1944 this boy, then 10 years of age, had an attack of acute rheumatic fever. Six months later, in the second week of May, 1945, he developed fever and anorexia, and petechiae on the legs shortly afterward. *Str. viridans* was discovered in a blood culture and penicillin therapy was instituted.

He was referred to Dr. Seinsheimer and admitted to Cincinnati Children's Hospital June 9, 1945. He appeared weak and pale but no petechiae were visible until the third day, when showers of them appeared on the chest and arms. The spleen was palpable but not greatly enlarged. A loud, blowing, systolic murmur was audible over the apical area of the heart and was transmitted to the entire left chest and axilla. Roentgenograms demonstrated no cardiac enlargement and an electrocardiogram was normal. The hemoglobin content of the blood was 9.0 Gm. per cent and there were 9300 leucocytes per cubic millimeter, of which 67 per cent were polymorphonuclear leucocytes. Blood cultures on the first and third hospital days were positive for *Str. viridans*.

Penicillin had been administered for six days before the patient was admitted to the hospital, and the total amount was not known. The drug was instituted again on June 11, 1945, in doses of 20,000 units intramuscularly every four hours, and then increased two days later to 35,000 units every three hours. During a period of thirty days, a total of 8,560,000 units were given. Transfusions of 250 c.c. of whole blood were given on three occasions.

On the seventh hospital day (June 18) the patient experienced a sharp pain in the left lower quadrant of the abdomen and tenderness was noted in the left flank. These symptoms disappeared after a few hours and recovery was otherwise normal. The urine was negative at all times except for an occasional trace of albumin. The hemoglobin levels rose to 15 Gm. per cent by the end of the month and the sedimentation rates which were slightly elevated on admission (0.63 mm. per minute) fell to normal (0.30 mm. per minute). The blood became

## BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN

DURATION OF THERAPY (DAYS)	METHOD OF ADMINISTRATION	OUTCOME	PERIOD OF OBSERVATION AFTER TREATMENT (MO.)
14	Intramuscular, intermittent, 12,500 units every 3 hours	Recovered	6
12	Intravenous, continuous drip, 120,000 units daily	Recovered	6
8	Intravenous, intermittent, 5,000 units every 4 hours	Died	
38	Intramuscular, intermittent, 20,000 units every 2 hours and later intravenous drip, 240,000 units daily	Recovered	12
27	Hypodermoclysis, continuous, 1,000,000 units total intra- venous, continuous drip, 200,000 units daily	Recovered	6
14	Intravenous, continuous drip, 300,000 units daily	Recovered	15
14	Intravenous, continuous drip, 300,000 units daily	Recovered	14
14	Intravenous, continuous drip, 300,000 units daily	Recovered	13
56	Intramuscular, intermittent, 25,000-30,000 units every 2 hours	Recovered	4
14	Oral, 100,000 units every 3 hours	Recovered	4
57	Intramuscular, intermittent, 10,000 units every 3 hours	Recovered	18
34	Intramuscular, intermittent, 25,000 units every 3 hours	Recovered	16
35	Intramuscular, intermittent, 25,000 units every 3 hours	Recovered	15
30	Intramuscular, intermittent, 20,000 units every 4 hours then 35,000 units every 3 hours	Recovered	12

sterile eight days after the penicillin therapy had been started in the hospital and remained sterile on seven subsequent cultures.

On Nov. 13, 1945, about four months after recovery, the child's tonsils and adenoids were removed. During a period of about five days after the operation, penicillin was administered intramuscularly in doses of 20,000 units every three hours until a total of 800,000 units were given. Blood cultures at that time and a month later were negative and the child has been free from symptoms of bacterial endocarditis for a period of twelve months since the onset of illness.

## COMMENT

Only one patient died and he had received only 240,000 units of penicillin. The others recovered without relapses or any evidence of vascular accidents after treatment was started. Children, in contrast with older patients, recuperate rapidly from acute infections and it is possible that endocardial lesions produced by the bacterial infection are less extensive in children and may be covered with epithelium rapidly after treatment is started. Likewise, the cardiac muscle of children may be able to withstand the strain of the infection or circulatory disturbance more readily than adults.

Dosage of 240,000 units proved inadequate. Two children of the group recovered after approximately one and a half million units had been given, but dosage varying from 4 to 11 million units was employed most frequently. It may be permissible to conclude at this time that not less than  $1\frac{1}{2}$  to 2 million units should be employed and that more will be required if the infection is severe or has been present for a long time, and if the patient's symptoms do not respond rapidly to the therapy. At least 200,000 units seems to be an adequate daily dose.



The method of administration of the drug seemed to be of little importance. Intermittent intramuscular injections were employed in our four patients and in two children reported previously. The child who received inadequate dosage and died likewise had the drug administered in this manner. The oral route was successful in one patient and in the remaining six children penicillin was given by continuous intravenous drip or by a combination of methods.

Other drugs do not seem to be necessary in the treatment of subacute bacterial endocarditis of children. Sulfonamides were employed in many of the early cases reported, including the first three of our four cases. It is well known that these drugs alone are relatively ineffective in the cure of bacterial endocarditis due to *Str. viridans*. Among the children treated with penicillin alone, the outcome has been excellent. Heparin was employed as an adjunct to the penicillin therapy of only one child. It does not seem to be necessary.

From this small group of fourteen children it is difficult to draw conclusions regarding prognosis or optimum therapeutic procedures. It is probable that many more children with subacute bacterial endocarditis have been treated with penicillin and it is hoped that the results will soon appear in the literature.

#### SUMMARY

The histories of four children with subacute bacterial endocarditis due to *Str. viridans*, who were treated with penicillin, have been reported in detail. The reports in the literature of ten other children treated in a similar manner have been reviewed.

Among this group of fourteen children only one died, and he had received inadequate dosage. A favorable outcome was achieved with total doses ranging from approximately 1.5 million to 11 million units of penicillin, administered in daily amounts of 80,000 to 300,000 units.

The route of administration seemed to make no difference in the outcome of this group of children, and no other drugs such as the sulfonamides or heparin seemed necessary.

#### REFERENCES

1. Collins, B. C.: Subacute Bacterial Endocarditis Treated With Penicillin, *J. A. M. A.* 126: 233, 1944.
2. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin, *J. A. M. A.* 127: 129, 1945.
3. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin: Second Report, *Ann. Int. Med.* 24: 170, 1946.
4. Goerner, J. R., Geiger, A. J., and Blake, F. G.: Treatment of Subacute Bacterial Endocarditis With Penicillin; Report of Cases Treated Without Anticoagulant Agents, *Ann. Int. Med.* 23: 491, 1945.
5. Flippin, H. F., Mayock, R. L., Murphy, F. D., and Wolferth, C. C.: Penicillin in the Treatment of Subacute Bacterial Endocarditis. A Preliminary Report on 20 Cases Treated Over One Year Ago, *J. A. M. A.* 129: 841, 1945.
6. Hirsh, H. L., and Dowling, H. F.: The Treatment of *Streptococcus Viridans* Endocarditis With Penicillin, *South. M. J.* 39: 55, 1946.
7. Burke, F. G., Ross, S. Walsh, B. J., and McLendon, P. A.: The Successful Use of Oral Penicillin in the Treatment of Subacute Bacterial Endocarditis; Report of a Case, *M. Ann. District of Columbia* 15: 22, 1946.

# PENICILLIN IN THE TREATMENT OF THE SYPHILITIC INFANT

## A PROGRESS REPORT

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THIS report on penicillin treatment of the syphilitic infant supplements the observations previously recorded.<sup>1,2</sup> In general, our enlarged experience confirms the initial impression that sodium penicillin given by intramuscular injection is a satisfactory treatment for the congenitally infected, syphilitic infant. This same experience has, however, caused us to modify our views concerning optimal treatment. This study is still in progress, and new interpretations and different emphases will arise as factual data accumulate. Nevertheless, a progress report seems desirable at this time.

We should like to point out that congenital syphilis is a severe and complex disease and should be considered apart from the acquired syphilis of the adult. It differs in its pathogenesis in that in congenital syphilis there is continual feeding of the spirochetes to the blood stream. The infection, involving all organs including bone, is more massive, intense, and serious because of interference in the rapid growth of tissues in the developing child. Other important differences are the immunologic immaturity of the fetus and the tendency to debility and secondary infection. The most acute stages of the disease are seen during the first few months of life, and it is especially during this phase that a higher mortality rate occurs because of the combination of intensity of infection by, and reaction to, the spirochetemia, and the concomitant debility and susceptibility to secondary infection. Treatment of infantile congenital syphilis is a far more complex problem than treatment of early syphilis in the adult, and requires the close cooperation of pediatrician and syphilologist.

## MATERIAL

Thus far we have treated thirty-six congenitally syphilitic infants\* with penicillin. Requirements for inclusion in this study are (a) a high or rising serologic titer for syphilis, and either (b) a clinically characteristic macular

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The results which are presented in this paper must be interpreted in the light of the fact that from June, 1943, the date of inception of the study, to the present, commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency in terms of units per milligrams has increased. The relative amounts of the several identified penicillin fractions G, F, X, and K, have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant, and that it may be significantly different today than it was originally. It is not now possible to assess the extent to which these changes may have affected the results here reported.

\*The Philadelphia General Hospital supplied eighteen of these infants, the Children's Hospital, eleven, the Pennsylvania Hospital, two; the Hospital of the University of Pennsylvania, four, the Saint Luke's and Children's Medical Center, one.

eruption usually accompanied by dark-field positive, papular or bullous lesions, or (c) roentgenographic evidence of inflammatory reaction in the metaphyses of the long bones, with or without periostitis. Every infant meeting these criteria was treated as soon as the diagnosis was established. There was one exception, a premature infant who arrived from another hospital, dehydrated, acidotic, and moribund, and who succumbed in a few hours. No infant was treated on serologic evidence alone except where the titer showed increasing values. With such a group of patients, the high mortality characteristic of syphilis in the congenitally infected infant, which is most marked in the first 2 or 3 months of age, was anticipated.

The mean age of all of our infants at the beginning of treatment was 2 months. Five of these infants were one month old or less, twenty-two were between one and 3 months, six were between 3 and 8 months, and three between 8 and 30 months. Thirty-three were Negro and three were white. There were fifteen males and twenty-one females. Seventeen had skin lesions considered to be characteristically syphilitic; eight were dark-field positive. Thirty had unequivocal roentgen evidence of syphilis, ranging from generalized osteochondritis to widespread periostitis.

Five had no roentgen evidence of syphilis. One (Case 345), age 7 weeks, showed no roentgen evidence because the maternal infection was acquired very late in pregnancy and the baby's infection was in its incipency as indicated by the rapidly mounting titer. Two (Case 328, 2½ years old and Case 368, 13½ months old) had passed the stage where early osseous lesions occur. The fourth (Case 148) was a very young infant 5 weeks of age, who had dark-field positive skin lesions and a high serologic titer but no evidence of osseous change. The father had secondary syphilis two months before the infant was born. The mother had a positive serologic reaction at the time of delivery. The fifth (Case 685) was a 13-week-old Negro infant, presumably infected very late in pregnancy. Two others (Case 392 and 63) had doubtful roentgen signs but unequivocal skin lesions and high serologic titers.

#### METHOD OF TREATMENT

The object of the study was to determine primarily what effect penicillin has in congenital syphilis, rather than to find the ideal dosage. A study of approximate dosage is now in progress, and obviously requires a larger series of cases.

Sodium penicillin was given intramuscularly every three hours over a period of seven days, then later over a period of fifteen days. At the outset, the individual doses were reduced for the first twelve or twenty-four hours, because of possible Herxheimer reaction. During the past year, however, no initial reduction in dosage has been used.

At first, we used the dosage approximately equivalent to 2,400,000 units for a 150 pound adult, or a total dosage of 16,000 units per pound of body weight. This dosage is similar to that employed in the study reported by Platou and his co-workers.<sup>3</sup> In the progress of our study it became obvious that this premise was untenable, and gradually this dosage was changed to 40,000, then 70,000

units per pound of body weight. Of the total cases, fifteen received dosages of sodium penicillin roughly in amount of 20,000 units or less per pound of body weight. Twenty-one received higher dosages while thirty-one received single courses. The plan of study was to have a monthly follow-up visit for complete physical examination by the pediatrician, blood drawn for serologic study, and repetition of the roentgenograms until they became normal. After the serologic reaction remained negative for six months, follow-up visits were planned at slightly longer intervals. Examination of cerebrospinal fluid, while not routinely done at the beginning of the study, is now being done at the onset and periodically after. No other antisyphilitic therapy was given. Supporting treatment in the form of fluids, transfusions and, electrolytes was an important consideration, especially in the younger and debilitated patients.

## RESULTS OF TREATMENT

*Clinical and Serologic Results.*—Clinical and serologic results are tabulated in Table I. In thirty-two of the thirty-six infants, the initial clinical response was uniformly good. Cutaneous and mucosal lesions healed rapidly and no positive dark-field examinations were found after twenty-four hours. Appetite, nutrition, and general activity improved. In those instances where clinical improvement was not manifest, the underlying difficulty was marked anemia, debility, or feeding difficulty associated with anorexia and vomiting or with marked nasal crusting and discharge from the nose.

The average time for the blood reagin titer to become negative was 260 days in those cases treated with less than 20,000 units per pound, whereas it was 154 days when the dosage was more than 20,000 units per pound of body weight. For statistical comparison of the two groups, the three older infants (Cases 88,

TABLE I. SEROLOGIC STATUS AT SPECIFIED TIMES

FOLLOW-UP AFTER START OF THERAPY	TOTAL CASES OBSERVED	CLINICALLY WELL				DEAD
		SERO- NEGATIVE	DECLINING	UNCHANGED	RE-TREATED	
Over 20,000 Units per Pound Body Weight						
60 days	12	0	4	5		3
120 days	8	2	4			
180 days	8	3	3*		1	
270 days	7	3	2			
365 days	6	5	0			
480 days	4	4				
599 days	1	1				
730 days	1	1				
Total	12					
Under 20,000 Units per Pound Body Weight						
60 days	21	2	5	5		3
120 days	16	5	5	4	1	1
180 days	11	6	1			
270 days	10	1				
365 days	8	8				
480 days	5	4				
599 days	2	2				
730 days	1	1				
Total	21					

\*Case 58.—Clinical relapse (dark-field positive skin lesions). Re-treated.

368, and 328, 23, 13½, and 30 months of age, respectively) were omitted. Thus the two groups were comparable as to mean age (2 months). Statistical comparison between the response of the two groups to treatment showed no significant difference. Clinically, however, it was our very definite impression that those infants treated with the higher dosages and especially the higher initial doses did better on the whole. This point, however, will need further observation on a greater number of cases. The serologic response is slower than that

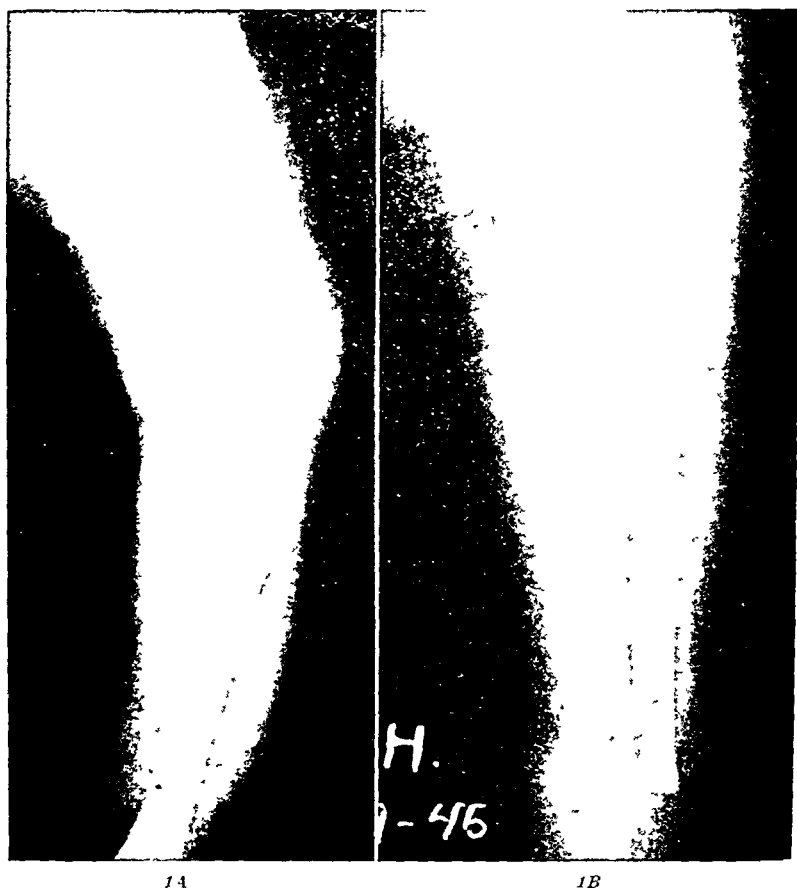


Fig 1A—W H., Feb 12, 1945. Age, 4 weeks. Children's Hospital of Philadelphia. Feeding problem. Positive serologic reaction for syphilis. Long bones reported as negative, left femur shows slight rarefaction at outer distal end of metaphysis which became more manifest on March 5.

Fig 1B—W H., March 9, 1945, at outset of treatment. Kline test 128 units of reagin. Age, 8 weeks, weight, 8 pounds, 6 ounces. There is destruction of the metaphysis of the left femur with obliteration of the normal architecture and a mushroom-shaped deformity. In the upper ends of the tibia and fibula the destructive process involves more of the medulla. Periosteal proliferation along the shaft is evident.

obtained in adults. This supports the statement that congenital syphilis cannot be considered to be a proportionately diminutive example of adult syphilis.

*Relapses.*—One infant (Case 58), whose treatment began at 3 months and amounted to 18,000 units per pound in an eleven-day period, showed marked clinical improvement and a steadily declining serologic titer on three follow-up

visits, yet at 177 days was found to have typical macular skin lesions which were dark-field positive. Re-treatment, using 67,000 units per pound in an eight-day period brought prompt clinical and gradual serologic improvement resulting in seronegativity 168 days later, which condition has remained for the year following.

This was the only clinical relapse. There was no instance of serologic relapse that was sustained. However, two infants (Cases 89 and 323) each showed one reversion to seropositivity before becoming consistently seronegative. Another infant (Case 328) became seronegative after re-treatment, then weakly seropositive just before it was lost to follow-up.



Fig. 1C.—W. H., March 20, 1945, eleven days after beginning treatment, using 5,000 units of penicillin every three hours, total, 560,000 units in fourteen days. Legs were swollen and painful on motion. The calcification is obviously being rapidly deposited in an area more extensively involved than was appreciated from preceding films. This rapid change has not previously been noted in the natural history of the congenitally infected syphilitic infant.

*Osseous Changes.*—Osseous changes as revealed in serial roentgenograms showed characteristic involution. There were three instances, however, where dactylitis, either mild or moderate, showed clinical and roentgen progression before regression. In two younger infants with marked osteochondritis (Cases 398 and 802, aged one and  $1\frac{3}{4}$  months respectively) the inflammatory process in and around the metaphysis became more easily demonstrable in the roentgenogram because of calcification. This, in all probability, is a part of the healing process.

*Re-treatment.*—Five cases were re-treated for various reasons. Four were in the low dosage group and occurred early in the study. The older infants were also in the low dosage group.

CASE 88.—A 23-month-old Negro female infant weighing 18 pounds had osseous and serologic evidence of syphilis, a marked "saddle nose," and malocclusion due to a short central maxilla. There was atrophy of the lower limb musculature, inability to walk, or even to stand. The knee and ankle jerks were exaggerated. Over a period of eleven days 16,000 units of penicillin were given without reaction. Improvement both roentgenographically and clinically followed. At 127 days after onset of treatment she was beginning to walk but still had slightly abnormal reflexes. Because the high serologic titer remained unchanged, she was re-treated at 356 days by administering 31,900 units per pound in eighteen days. The clinical improvement continued while the serologic response was less prompt. When last seen at 678 days, the serologic titer was still two Kline units. Cerebrospinal fluid was at no time abnormal.

CASE 328.—A 30-month-old Negro girl had a mild degree of congenital syphilis as indicated by a Kline titer of 64, generalized lymphadenopathy, and splenomegaly. She received 18,750 units per pound of body weight in seven days. The serologic titer remained between 64 and 128 Kline units, so re-treatment was begun at 215 days with 67,400 units per pound in a fifteen-day period. At 331 days the infant was seronegative for the first time, but at 371 days showed 32 Kline units of serum reagin. The case was thereafter lost to follow-up.

CASE 199.—An 8-month-old female weighing 15 pounds, 1½ ounces, had serologic and roentgen evidence of syphilis. The outstanding physical finding was hydrocephalus. The head was so large that she was unable to lift it or sit alone. Aside from nystagmus the neurologic examination was negative. Over a period of seventeen days, 16,060 units per pound of body weight were given without reaction. During the month following onset of penicillin therapy there was a marked regression in hydrocephalus, the head circumference receding from 22 inches to 19 inches with overriding of the bony plates (normal circumference 17 to 18 inches). The chest circumference remained the same. The child became more alert, more active, and gained weight, yet the serologic titer remained stationary. The osseous lesions showed marked improvement by roentgenogram. Because of the low initial dosage, and in hopes of accelerating the serologic response and clinical improvement, she was re-treated at sixty-five days, using 19,120 units per pound over a five-day period. At 186 days after the initial therapy (age 14 months) she was sitting alone, and at 256 days became seronegative and remained so throughout the observation period lasting 536 days. The spinal fluid had never shown any abnormality. At the time of last examination she seemed normal in every way.

CASE 58.—A 3-month-old Negro male infant with marked initial clinical infection, a blood serologic titer of 128 Kline units, and roentgen evidence of involvement of the long bones, received 18,500 units per pound of body weight over a nine-day period. The clinical response was prompt and serial serologic tests showed a declining titer, yet at follow-up when 177 days old he showed scattered macular skin lesions which were dark-field positive. He was re-treated with 67,600 units per pound of body weight over an eight-day period with no untoward reaction. His serologic titers were slightly higher for the next three months but he became seronegative on the three hundred and forty-fifth day, and had remained so when last observed on the six hundred and fifty-third day. There was no history to suggest a re-infection.

CASE 398.—A one-month-old Negro female infant weighed 5 pounds, 3 ounces at birth and 5 pounds, 5 ounces when admitted. She was in a severe state of debility, showed signs of pneumonia and generalized desquamation of the skin. There were roentgenographic signs of periosteal involvement of all long bones, and considerable osteochondritis. The Kline titer was 128 units. During the eight-day course of treatment when she received 22,600

units per pound of body weight, there was rapid calcification in the previously existing inflammatory process in the bone. Transfusions of blood and plasma were required, and improvement was slow. At the age of 2 months she still weighed only 6 pounds, one-fourth ounce and had extensive bone changes and a Kline titer of 256. At the age of 3 months, when the Kline titer was still unchanged and the infant was still in a poor nutritional state weighing  $7\frac{1}{2}$  pounds, it was decided to re-treat, because at that time the dosages appeared to be far too low. She received 40,000 units per pound over a sixteen-day period beginning sixty days after her first course of therapy. Clinical improvement was prompt and marked. Within a month she gained almost 4 pounds. At 155 days she was seronegative and remained so throughout her 372-day observation period.

*Fatalities.*—Since the two fatal cases mentioned in our previous report we have had five additional deaths, making a total of seven or 19.4 per cent.

CASE 47.—A Negro, female, premature infant weighing 3 pounds,  $14\frac{1}{2}$  ounces at birth, was the first child of an untreated seropositive mother. The infant had "snuffles," enlargement of the liver and spleen, periostitis of the bones roentgenographically demonstrated in the right arm and leg, and serologic reaction of 64 Kline units. She also had signs suggesting a congenital cardiac defect, probably patent ductus arteriosus. A seven-day period of treatment was given, with 18,000 units per pound of body weight. Half doses were given for the first twenty-four hours. There was a rise of temperature to  $100.5^{\circ}$  F. twelve hours after treatment started, but the baby showed no other untoward signs. One week after completion of therapy, notwithstanding general clinical improvement, the infant developed diarrhea, and despite active treatment died four days later on the seventeenth day after onset of penicillin therapy, when 35 days old. There had been a case of diarrhea in the same nursery three weeks previously, at which time all contacts received 0.5 c.c. immune human serum globulin.\* Post-mortem blood culture showed hemolytic *Staphylococcus aureus*. No autopsy could be obtained.

CASE 112.—A 6-week-old Negro female infant weighing 8 pounds, 3 ounces, had "snuffles," generalized adenopathy, enlargement of liver and spleen, enlargement of the epiphyses at the wrists, and partial paralysis of the left arm. There were extensive osseous changes. On admission the temperature was  $102^{\circ}$  F. and ranged from  $100$  to  $104^{\circ}$  F. for the first three days. The hemoglobin was 53 per cent. Penicillin therapy was begun the third day after admission. Thereafter, the temperature was normal but anorexia persisted and diarrhea manifested itself intermittently. Only one-half of the calculated penicillin dosage of 70,000 units per pound was given, as the course was steadily downhill and the infant expired on the ninth day of treatment. The first three doses were only one-tenth the subsequent doses. Fever of  $101^{\circ}$  F., present for the first two days after admission, persisted for another twenty-four hours after treatment started, then fell to normal and remained there. The infant showed no immediate reaction to treatment. Autopsy showed generalized osteochondritis, hyperplasia of spleen, and aspirated debris resembling milk curds in the bronchial tree.

CASE 286.—An emaciated, ill, dehydrated, 5-week-old, Negro female infant weighed 5 pounds, 10 ounces (birth weight 5 pounds, 11 ounces) when transferred from another hospital where she had been treated for bronchopneumonia. She was delivered at eight months of a mother with untreated syphilis. Previous roentgenograms showed extensive osseous involvement. The Kline titer was 128 units. The infant showed respiratory distress but no signs of pneumonia. The hemoglobin was 29 per cent, leucocytes 28,200. Penicillin was begun using 350 units every three hours, and the child gradually became weaker and died after the fifth injection. Autopsy revealed diffuse bronchopneumonia and there was also moderate periportal fibrosis in the liver and diffuse hyperplasia of the spleen.

CASE 397.—A 3-month-old, Negro male infant, born at term of an inadequately treated syphilitic mother, weighed 7 pounds, 4 ounces at birth. The admission weight was 8 pounds,

\*This was being used experimentally in a study of its protective value in epidemic diarrhea of the newborn. No positive evidence of value was obtained.



6 ounces. He had seemed well until twenty four hours before admission to another hospital, when he developed fever, cough, and purulent nasal discharge. The infant was emaciated, had physical signs of pneumonia, macular lesions on the skin, extensive characteristic changes on the roentgenograms of the long bones, and strongly positive Kolmer and Kahn reactions. The temperature on admission was 105° F. After two days of sulfadiazine the chest signs cleared and penicillin was given over a period of ten days, 26,000 units per pound of body weight. The first ten doses were reduced to 250 units each. The baby improved somewhat at first but on about the tenth day of therapy began to vomit, became listless, and had intermittently loose stools. Penicillin was discontinued. Despite parenteral fluids, plasma, blood transfusions, and careful dietetic management, his distention and diarrhea continued. He developed an otitis media. The course was downhill and he died twenty seven days after the onset of penicillin treatment. Roentgenograms taken post mortem showed some healing of the extensive osteochondritis. Permission for autopsy was not granted.

CASE 507.—A one month old Negro female infant weighed 5 pounds, 2 ounces at birth. The mother was incompletely treated for syphilis during pregnancy. On admission, the infant weighed 5 pounds, was in poor condition, and showed marked roentgen and serologic evidence of syphilis. The initial doses of penicillin were 500 units every three hours for the first thirty nine hours, 1,000 units every third hour for the next three doses, and thereafter, 2,000 units at each dose. There was no immediate reaction. Transfusions of blood and plasma and parenteral fluids were given for the first few days until improvement was manifest. The total dosage averaged 36,300 units per pound of body weight and was completed in a period of thirteen days when the patient was discharged in good condition. Later it was learned that she died thirty days after onset of penicillin treatment, having been brought into the receiving ward of another hospital in a moribund state. Malnutrition was the ascribed cause of death. There was no autopsy. This was an illegitimate and unwanted child and family cooperation had always been poor.

CASE 552.—An 11 week old, debilitated, Negro female infant was admitted weighing 7 pounds, 8 ounces. She had extensive desquamation and macular skin lesions, "snuffles," paresis of the left arm, marked periostitis and osteitis by roentgenogram, and a serologic titer of 256 Kline units. The hemoglobin was 45 per cent. Penicillin was begun, using a total dosage of 37,300 units per pound of body weight. There was no initial reduction, each dose being 5,000 units, given every three hours. No immediate reaction occurred. Two blood transfusions were given so that during the first three days of treatment the hemoglobin rose to 72 per cent. There was marked clinical improvement. Then the "snuffles" became more marked, the infant took feedings poorly, vomited occasionally, and had intermittent loose stools. The infant failed progressively and died on the seventh day of treatment, having received one half the calculated dosage. Spinal fluid collected immediately post mortem showed the protein to be 75 mg per 100 c.c., and tests for syphilis by the Wassermann and mastix technique were strongly positive. Post mortem blood samples showed a blood urea nitrogen of 65 mg. per 100 c.c. Autopsy showed injected mucosa of the terminal ileum and colon, generalized inflammatory changes in the mesenteric lymph nodes, and some aspirated debris in the bronchial tree with partial atelectasis. There was also marked proliferation at the epiphyses of the wrists, the only long bones examined.

CASE 299.—A well nourished, 6 week old, Negro male infant weighed 9 pounds, 7 ounces. His mother was unmarried, had contracted syphilis late in pregnancy, and had received no treatment. There was a two week history of "snuffles" and eruption on the palms and soles, which proved to be dark field positive. Hemoglobin was 47 per cent and rose to 57 per cent after two transfusions. Penicillin was administered over a period of twelve days, the dosage being 61,540 units per pound of body weight. The immediate response and general clinical course were good, with the exception of development of clinical evidence of extensive dactylitis. Roentgenograms showing marked periosteal changes on the sixth day of therapy, at which time there was also microscopic hematuria, some albuminuria, and a few casts, while the blood showed 5.1 Gm. of protein and 10 mg. urea nitrogen per 100 c.c.

The dactylitis gradually receded. Roentgenograms which were negative on admission showed the appearance of the inflammatory changes of periostitis and osteochondritis, in the long bones and metacarpals followed by gradual healing. The infant left the hospital twenty-eight days after the onset of therapy in good general condition, the only abnormality being slight but firm swelling of the fingers. He was seen at frequent intervals during which time his improvement continued and his serologic reagin titer declined steadily. He was brought in with a mild respiratory infection, temperature  $100.6^{\circ}\text{F}$ ., history of nasal discharge for two days, and anorexia for one day. There were some rhonchi in the chest but since the infant seemed only mildly ill, he was given the usual directions for fluids, nose drops, feedings, and sulfadiazine, 0.13 Gm. every four hours. Later it was learned that he became much worse and died at home two days after he had been seen at the hospital. There was no autopsy.

During the course of this study it was noted that occasional infants with congenital syphilis showed signs of toxemia as manifested by anorexia, diminishing activity, and occasionally diarrhea. This has also been noted in arsenotherapy. Whether or not it is a Herxheimer reaction alone or whether it should be considered inherent to the disease cannot be stated. With our increasing experience the latter seems more likely. However, attention is called to the fact that it does occur, and, as such, may offer a serious complication of which one should constantly be aware in order to anticipate and offset further complications. It is to be pointed out that when intercurrent infection is present (e.g., from staphylococcus or pneumococcus) the dosage of penicillin normally used for syphilis is insufficient to care for these complications. This is especially the case if the initial dose of penicillin is reduced in infants to prevent the so-called Herxheimer reactions. It is noteworthy that this study was begun anticipating such reactions, but, since even the occasional rise of temperature occurring within the first few hours did not prove harmful, the small initial dosage was abandoned and the tendency has been to increase the total dosage and lengthen the treatment period.

It is our feeling that in some infants the lower initial dosage may be more harmful to the infant than the higher initial dosage, in that any secondary infection which may be present is not cared for, even though the syphilis may be favorably influenced. The older antisypilitic remedies (e.g., neoarsphenamine, Mapharsen and bismuth) had little direct effect on intercurrent infection. For the first time with penicillin we have a drug equally effective against syphilis, pneumonia, and other forms of localized pyrogenic infection and septicemia. In determining the dosage to be used, the total picture of infection of the infant should be considered, and the dosage regulated accordingly. Less satisfactory results are obtained by considering penicillin therapy for syphilis only.

Our fatal cases illustrate the necessity of active supportive treatment during the penicillin therapy period. One of the recent patients (Case 763) was an emaciated, dehydrated infant weighing 5 pounds,  $3\frac{3}{4}$  ounces, who responded well for the first two weeks, but after completion of penicillin therapy became much worse clinically. "Snuffles" and nasal crusting made breathing and feeding difficult. She was listless and had occasional diarrhea. It was only vigilant pediatric nursing that prevented her demise. The need for special nursing care of the debilitated syphilitic infant cannot be overemphasized.

Had penicillin therapy been withheld until each patient was put in optimal condition by the addition of blood, plasma, electrolytes and fluids, more infants would have died *before* penicillin treatment and consequently would not have been included in this study. Under such conditions the number of fatalities would have been lower.



Fig 2A.—J S, March 22, 1946. Lower extremities Age, 6 weeks Philadelphia General Hospital. Strongly positive serologic test for syphilis Thighs seemed normal in size and motility, zone of rarefaction evident beneath ends of metaphyses with fragmentation of the metaphyseal-epiphyseal line, and in some instances a mushroom-shaped deformity thought to be due to multiple infarctions.

Four of the five deaths occurring during treatment were during the earlier months of this study. It is our feeling that death was not directly related to the penicillin, but rather to the combination of the underlying poor condition of the syphilitic infant and intercurrent infection. Better pediatric management is essential in reducing such mortality. In the two infants who died outside the hospital, it would seem that one death (Case 299) was due to an overwhelming respiratory infection and the other (Case 507) due to the malnutrition of maternal neglect with perhaps an unrecognized concurrent infection. Neither was related to penicillin or to the congenital syphilis directly.

The infrequency of relapse is noteworthy. It raised the question of a different immunologic relationship between the infected mother and the fetus.

2B.



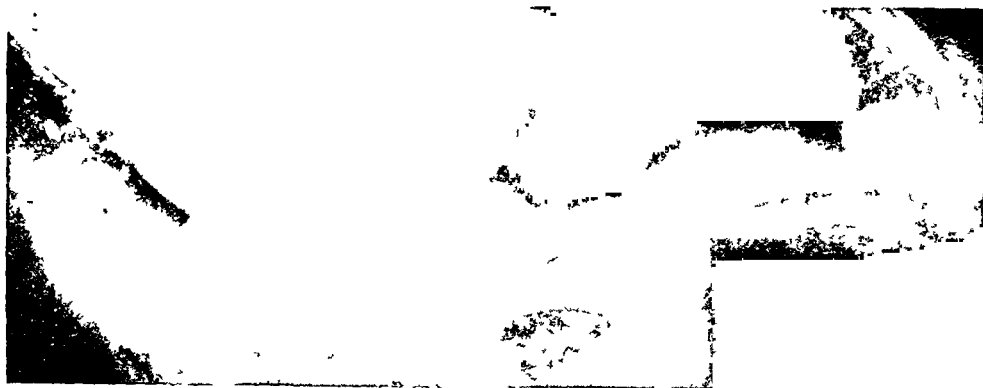
2C.

Fig 2B—J. S., April 10, 1946. Lower extremities. Three days after completion of treatment (1.04 million units of penicillin from March 25, 1946 to April 7, 1946), the thighs became markedly swollen and painful. Patient assumed a constant frog-like position. Roentgenogram shows rapid, unexpected appearance of excessive calcification in soft tissues in proximal portion of right femur.

Fig 2C—J. S., April 26, 1946. Lower extremities, nineteen days after completion of treatment. More periosteal proliferation and less of the denser, more massive lesions at the proximal ends of the femora are seen.

In acquired syphilis of the adult treated with penicillin, the cumulative failure rate caused by relapse or reinfection reaches 15 per cent after eleven months.<sup>4</sup> It is of interest to note that in our admittedly small number of cases of congenital syphilis, no relapse was observed within one year after adequate treat-

2D



2L

Fig 2D—J S. March 22, 1946 Upper extremities, before treatment

Fig 2L—J S. April 10, 1946 Upper extremities, three days after completion of treatment. Increased calcification at proximal end of right humerus and generalized periosteal proliferation are evident.

ment. This difference between acquired and congenital syphilis under penicillin treatment seems to indicate two possibilities (1) the high cumulative failure rate in acquired syphilis is due more to reinfection than to relapse, and (2) congenital syphilis after treatment with penicillin produces more permanent immunologic resistance than acquired syphilis under similar conditions. More prolonged and better controlled observations on a larger series of cases of congenital and acquired syphilis will give us the final choice between these two important possibilities, both from a theoretical and a practical point of view.

A special point of interest is the intensity and rapidity of osseous changes following administration of penicillin in some of our cases (Cases 802, 338, 299, and 763).

More rapidly progressive destructive and proliferative lesions may become evident in the long bones of infants with congenital syphilis under the influence of penicillin. They are very reminiscent of similar pictures observed in acute pyogenic osteomyelitis, although in their pathogenesis and etiology they are different. In both instances, the pathologic reaction is primarily due in the first place to rapid destruction of spirochetes or staphylococci with elimination of necrotic debris, and to periosteal and soft tissue inflammatory reaction which is then closely followed by osseous repair.

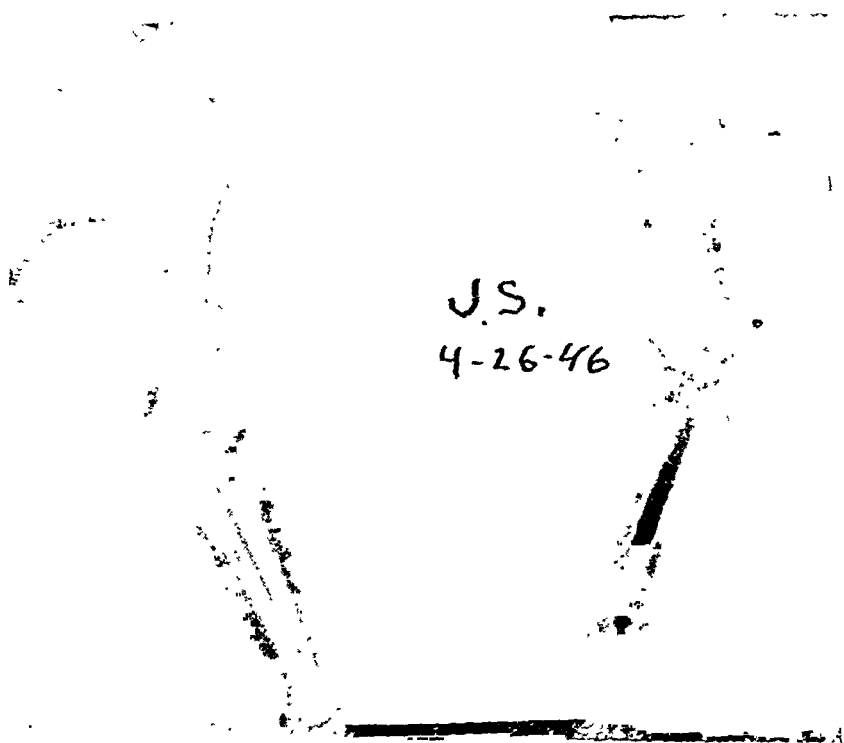


Fig. 2F.—J. S., April 26, 1946. Upper extremities, nineteen days after treatment finished. Previous extensive calcification has disappeared, periosteal changes still evident.

In analogy to the roentgen findings in acute pyogenic osteomyelitis,<sup>5</sup> calcification may become apparent in congenital syphilis following treatment with penicillin, through very extensive osteoblastic activity of the periosteal layer around the metaphyses of the long bones, especially of the femur or humerus. Such calcification, bearing some resemblance also to calcified subperiosteal hemorrhages in scurvy, appears very early after treatment and leads to very marked temporary deformity of the bones (Fig. 1). At first the calcification may be very irregular and may give the false impression that it involves also the surrounding soft tissue. Repair is rapid and progressive. (Fig. 2.)

DATA ON THIRTY-SIX INFANTS WITH CONGENITAL SYPHILIS TREATED WITH PENICILLIN\*

CASE	AGE IN MO.	CLINICAL EXAM.			S.T.S. IN KLINE UNITS	NUTRITION STATUS	WT. IN LB. AND OZ.	PENICILLIN UNITS PER POUND	PENICILLIN—INTRAMUSCULAR ALIQUOT DOSES EVERY 3 HR.			CLINICAL RESPONSE	DAYS POST-PEN. FIRST SUS-TAINED NEG. S.T.S.	NO. DAYS FOLLOWED	COMMENT	
		SKIN	FIELD	X-RAY					TOTAL DOSE	IN DAYS	REDUCED INITIAL DOSE					ACTION
<i>Total Dosage—Less Than 20,000 Units of Penicillin per Pound Body Weight</i>																
43	1½	+	+	+	64	Poor	6—3	16,129	100,000	9	✓	Good	100	297	17	Premature; probable congenital cardiac defect; general debility; slight improvement, then diarrhea; died at age 35 days; no autopsy
47	7½	0	+	+	128	Poor	4—7½	18,099	80,000	7	✓					
58	3	0	+	+	128	Poor	12—11	18,373	236,000	11	✓	Rash	Good	345	653	Relapse; developed dark-field positive lesions while bones and S.T.S. improving; re-treated at 177 days; 1,200,000 units in 8 days
63	4	0	±	+	Pos. Not Quantitative	Poor	12—14	18,615	242,000	9	✓	?		207		Gradual decline in S.T.S. titer to 4 units; lost to follow-up
88	23	0	+	+	32	Fair	18	16,000	288,000	11	✓	Good		678		Re-treated after 386 days; seroresistance 930,000 units in 18 days—S.T.S. ± but marked clinical improvement
89	4	0	+	+	64	Poor	7—11	18,440	142,000	10	✓	Good	199	608	8	Died during treatment; acute nutritional disturbance; autopsy, bronchopneumonia
112	1½	0	+	+	128	Poor	7—11	10,631	111,625	8	✓					
113	1¾	0	+	+	128	Fair	9	11,111	100,000	7	✓	Good	217	459		
155	2	+	+	+	128	Good	11—11	16,410	192,000	6	✓	Temp. 101—102° F. 5th day	Good	96	461	

\*Total dose computed on basis of weight, administered intramuscularly every third hour in aliquot doses, except where indicated smaller initial doses were employed.

	199	8	0	+	64	Fair	15—	14	16,060	240,950	17	V	Good	256	536	Re-treated after 65 days, 350,000 units, to facilitate already improving hydrocephalus
207	3	+	+	+	128	Poor	8	16,094	128,750	15	V	V	Good	287	483	Died during treatment; debility, anemia; autopsy, bronchopneumonia, hepatitis
286	1½	0	+	+	32	Poor	5—10	310	1,750	2	V	V	Good		2	
328	30	0	-	-	64	Fair	24	18,750	150,000	7			Good		371	Re-treated after 215 days, 1,800,000 units in 15 days, for S.T.S. improvement; Kline, 32 units at 371 days
343	3	+	+	+	128	Good	9—13	17,755	174,000	8			Good	165	165	Lost to follow-up; Kline, 64 units at 59 days
368	13½	+	-	-	64	Good	24	14,581	390,960	8			Good	59	59	Lost to follow-up; Kline, 64 units at 59 days
					Total Dosage—More Than 20,000 Units of Penicillin per Pound Body Weight											
87	1½	+	+	+	128	Poor	3	26,667	91,000	14	V	V	Good	224	576	Marked debility; good response
148	1½	+	+	+	128	Poor	6—8	22,246	144,600	15	V	V	Good	217	626	
285	1¼	+	+	+	128	Fair	8—2	74,000	601,200	15	V	V	Good	156	358	
293	4	+	+	+	64	Good	11—8	52,087	600,000	7	V	V	Good	363	363	S.T.S. doubtful at 196 days; no follow-up until 363 days
299	1½	+	+	+	32	Good	9—12½	61,510	600,000	12	V	V	Good		93	Excellent clinical response; later died at home; no autopsy
323	3	0	+	+	128	Poor	9—1½	26,373	240,000	13	V	V	Good	180	298	S.T.S. negative at 111 and 139 days; 32 units at 160 days
344	½	+	+	+	32	Good	7—7	21,570	159,600	7			Good	69	411	
345	2	+	-	-	128	Good	7—8½	20,000	150,000	7			Good	47	474	
397	3	+	+	+	Pos. Not Quantitative	Poor	8—6	24,837	202,400	10	V	V			27	Died; bronchopneumonia; septicemia, otitis; no autopsy
392	1	+	±	±	128	Fair	6	20,000	120,000	8			Good		81	S.T.S.; Kline, 16 units when lost to follow-up



DATA ON THIRTY-SIX INFANTS WITH CONGENITAL SYPHILIS TREATED WITH PENICILLIN—CONT'D

CASE	AGE IN MO.	CLINICAL EXAM.		S.T.S. IN KLANE UNITS	NUTRITION STATUS	WT. IN LB. AND OZ.	PENICILLIN UNITS PER POUND	PENICILLIN—INTRAMUSCULAR ALIQUOT DOSES EVERY 3 HR.				CLINICAL RESPONSE	DAYS POST-PEN. FIRST SUS-TAINED NEG. S.T.S.	NO. DAYS FOLLOWED	COMMENT
		SKIN	FIELD	DARK	BONE	X-RAY	TOTAL DOSE	IN DAYS	REDUCED INITIAL DOSE	RE-ACTION	Shock, 4 hr.				
398	1	0		+			22,641	120,000	8		Shock, 4 hr.	Good	155	372	Re-treated after 60 days to accelerate improvement
507	1	0		+			36,320	181,600	13	✓		Good		30	Good initial response; later, died at home; no autopsy
508	8	0		+			38,071	750,000	16			Good	106	279	
513	2	+		+			35,789	272,000	15	✓	Rash	Good	108	262	
517	2½	+		+			36,252	286,400	19	✓	Temp. 102° F. after 2nd	Good		74	
552	2½	+		+			37,333	280,000	7	✓				7	Died during treatment; acute nutritional disturbance; autopsy
685	3¼	0		-			69,084	759,924	15			Good	31	129	
756	2	0		+			66,977	720,000	16			Good		63	
758	1¾	0		±			70,244	720,000	16		Temp. 102° F. after 8 hr.	Good		39	
763	1¾	0		+			74,913	393,204	16			Slow		60	Stormy course; marked debility; final improvement before discharge
802	1¾	0		+			65,882	560,000	15		Temp. 101° F. after 3rd dose	Good		15	

## REACTIONS

The reactions observed and associated with treatment were predominantly of three types, fever, skin eruptions, and those associated with accelerated osseous involution. (Table II.) Febrile reactions occurred in seven of the thirty-six infants and were usually seen within the first six to eight hours. They were of short duration and in only one infant (Case 293) associated with systemic signs. This infant showed generalized edema, hematuria, and a temperature of 102° F. six hours after onset of therapy. The temperature returned to normal in several hours. The other signs disappeared the next day.

TABLE II. REACTIONS TO PENICILLIN THERAPY

CASE	AGE (MONTHS)	UNITS OF PENICILLIN	TIME OF REACTION	TYPE OF REACTION
398	1	4,000	4 hours	Shock; temperature 94° F.
345	2	5,000	1 hour	Temperature 104° F.; rash
293	4	3,000	6 hours	Temperature 102° F.; edema; hematuria
517	2½	1,000	6 hours	Temperature 102° F.
758	1¾	18,000	7 hours	Temperature 102° F.
802	1¾	15,000	8 hours	Temperature 101° F.
392	1	12,000	15 hours	Temperature 101° F.
58*	10½	175,000	30 hours	Rash
513	2½	19,500	60 hours	Rash
155	2	114,900	5 days	Temperature 102° F.
299	1½	256,000	6 days	Dactylitis

\*Re-treatment

The skin eruptions were of a maculopapular nature, appeared between six and sixty hours in the three patients where noted, and were transient. They were most probably accentuations of syphilitic lesions induced by therapy (cutaneous Herxheimer).

One infant (Case 398) became hypothermic, limp, and was in a state of mild circulatory collapse within four hours after the first dose of penicillin.

One infant (Case 249) showed marked dactylitis on the seventh day after treatment commenced.

Two other infants (Cases 756 and 758) showed exacerbation in the dactylitis already present at onset of therapy.

The four infants in which the usual initial clinical improvement was not manifest were already in very poor condition, yet showed no untoward reactions which could be related directly to therapy.

In no case was there any direct relationship between age of patient, amount of penicillin, and time of reaction. More recent experience has proved that the so-called Herxheimer reaction is not to be feared and that in the debilitated infants, as mentioned before, it is even more desirable to give larger initial dosages to offset possible secondary infection.

Occasionally diarrhea was encountered during therapy, but in about the same incidence as in other nonsyphilitic patients receiving no penicillin.

## SUMMARY

Thirty-six infants with congenital syphilis were treated with intramuscular penicillin in dosages ranging from 11,000 to 75,000 units per pound of body weight over periods of seven to fifteen days.

Fifteen received total dosages of less than 20,000 units per pound of body weight, twenty-one received over 20,000 units per pound of body weight. When three older infants were removed from the lower dosage group, and the two groups were statistically comparable, there was no significant difference in results. The only case of clinical relapse, however, and three other cases meriting re-treatment, occurred in the low dosage group. The impression was that clinical improvement occurred more rapidly with the higher dosages.

Nineteen have become clinically well and seronegative.

Six became clinically well, but remained seropositive. Three were seropositive when lost to follow-up at 74, 59, and 81 days after beginning treatment, and two were clinically well but serologically doubtful. Four of these six patients were in the lower dosage group.

Seven died, five while hospitalized for penicillin therapy, two much later after initial clinical improvement.

Four have been treated too recently to evaluate beyond the prompt clinical improvement.

There was no case of serologic relapse in the whole group, and only one clinical relapse, which was in the group receiving the lower dosage.

#### CONCLUSIONS

From observations during this study the following conclusions seem tenable:

1. The recommended total dosage of sodium penicillin is not less than 75,000 units per pound of body weight, given intramuscularly every three hours in aliquot doses, and the treatment course should not be less than fifteen days.

2. There is no need for an initial low dosage, even in debilitated infants. Higher dosages seem helpful in combating secondary infection.

3. There are cases manifesting symptoms referable to toxemia (anorexia, weakness, vomiting, occasionally diarrhea) where serious complications can be avoided only by anticipation, early hospitalization, and prompt and vigilant pediatric supervision.

4. Syphilis is a different and more serious infection in the congenitally infected infant than in the early acquired infection of the older person, and as such it is a problem requiring the closest cooperation between the pediatrician and the syphilologist.

5. The optimum time dosage relationship is still to be worked out.

#### REFERENCES

1. Lentz, J. W., Ingraham, N. R., Jr., Beerman, H., and Stokes, J. H.: Penicillin in the Prevention and Treatment of Congenital Syphilis, *J. A. M. A.* 126: 408, 1944.
2. Ingraham, N. R., Jr., Stokes, J. H., Beerman, H., Lentz, J. W., György, P., and Rose, Elizabeth K.: Penicillin Treatment of the Syphilitic Infant, *J. A. M. A.* 130: 694, 1946.
3. Platou, R. V., Hill, A. J., Ingraham, N. R., et al.: Penicillin in the Treatment of Infantile Congenital Syphilis: A Brief Feeler and Note, *J. A. M. A.* 127: 582, 1945.
4. (a) Moore, J. E., Mahoney, J. F., et al.: The Treatment of Early Syphilis With Penicillin, *J. A. M. A.* 126: 67, 1944.  
(b) Leifer, William: The Treatment of Early Syphilis With Penicillin, *J. A. M. A.* 129: 1247, 1945.  
(c) Committee on Medical Research and the U. S. Public Health Service, *J. A. M. A.* 131: 265, 1946.
5. Altemeier, W. A., and Helmsworth, J. A.: Penicillin Therapy in Acute Osteomyelitis, *Surg. Gynec. and Obst.* 81: 138, 1945.

# METHEMOGLOBINEMIA

## TWO CASES IN NEWBORN INFANTS CAUSED BY NITRATES IN WELL WATER

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### CASE HISTORIES

CASE 1.—V. C. G. was a girl 5 weeks old. Her family and prenatal history were not contributory. She was fed with a powdered milk formula.

On April 3, 1945, the family doctor gave her a prescription for a mild cough.

On April 4, she did not enjoy her feedings and looked a little unwell.

On the morning of April 5, the mother found the infant rather cyanosed. During the same day she drank very poorly and had about ten yellow stools, which became progressively more liquid. The condition grew worse from hour to hour, and the child was hurried to the clinic in the evening.

*Physical Examination.*—Good nutrition. Slate-colored cyanosis of the whole body, more marked on face and hands, more evident when the child cried. No icterus. On the whole, the infant presented the appearance of complete apathy. The respiratory rate was 90 per minute; the pulse, 200. Rectal temperature was  $36.2^{\circ}\text{C.}$  ( $97.2^{\circ}\text{F.}$ ). There was no movement of the nostrils with respiration, and no dehydration. The spleen and the liver were not felt. The lungs and the throat were normal. The heartbeat was regular and accelerated. Its volume was normal. The heart sounds were of good quality. No murmurs were heard.

Inasmuch as a diagnosis of sepsis was entertained, blood was drawn for culture. This blood was of normal fluidity, but its color was frankly chocolate brown. It was not hemolyzed. It contained large amounts of methemoglobin, but no quantitative study was made. From the color of the blood it was thought that the methemoglobin constituted about 50 per cent of the total pigment. We decided to transfuse the patient. In the course of preparation for transfusion, the condition became really alarming. When we cut the skin to denude the vein, the child did not cry. She received 30 c.c. of citrated blood. After a few minutes her condition was much better; her respiration was less irregular, her pulse less rapid, and the cyanosis less marked. The improvement was more obvious on the next day. The color of the skin was almost normal. There was no more dyspnea. The blood was brown red, and contained much less methemoglobin. The appetite was good, and the stools were normal in number and consistency. Blood, 30 c.c., was given again intravenously. Forty-eight hours after the first signs of illness, the symptoms were completely absent. There was no more methemoglobin present in her blood, and her skin had a normal color.

*Laboratory Data.*—Laboratory data at the time of admission to the clinic were as follows:

Blood: Hemoglobin, 75 per cent; white blood cell count, 45,000. Differential count: neutrophils, 63; lymphocytes, 24; monocytes, 2; metamyelocytes, 9; plasmocytes, 2. A few toxic neutrophils. The bone marrow smears were normal. The day after the first transfusion the white blood cell count was 18,000.

Urine, no abnormal findings.

Stools, no fat or starch or parasites.

Serum bilirubin, 0.68 mg. per cent.

The blood culture gave no growth.

Blood-urea 20 mg. per 100 c.c. Bleeding and coagulation times were normal.

We did not search for nitrites in the blood nor for nitrosobacilli in the stools.

The toxicologic analysis on the cough medicine and on samples of the milk powder gave negative results. The child did not wear clothes dyed with aniline.

From the Institut de Pédiatrie (Prof. L. Madaugue) University of Louvain,

The well water used for the dilution of the formula contained 497 mg.  $\text{NO}_3$  per liter and 0.114 mg.  $\text{NO}_2$  per liter. The well was two meters away from the cesspool. Bacteriologic examination of the water revealed the presence of colibacilli and enterococci about 700 per c.c. The parents stated that the water was boiled before its use. No other members of the family were ill from this water. Following recovery of the patient, the well water was omitted from the baby's formula. We saw the child eight months later. Her growth was normal and uneventful and she looked perfectly well.

CASE 2.—D. O. was a girl 1 month of age. Her family and prenatal history were not contributory. Since birth she had received powdered milk diluted in well water in good proportions. When she was 15 days of age, she became suddenly rather cyanosed, but her general condition seemed to be good, and on the following day she regained her normal appearance. Five hours before this child was rushed to the hospital, the mother had noticed the appearance of a cyanosis considerably more marked than in the first episode. The infant had refused her feedings. Her stools were normal.

*Physical Examination.*—There was striking coloration of the skin and of the mucosae, quite similar to the former case in severity and in distribution. The pulse rate was 175 per minute. The respiration rate was 78. There was no movement of the alae nasi. Otherwise, the clinical examination was normal.

The venous blood was chocolate brown and contained large amounts of methemoglobin and about 100 gammas of nitrites per 100 c.c. The urine was normal. The blood contained 60 per cent hemoglobin, 2,660,000 red blood cells, 27,900 white blood cells. Differential count: neutrophils 25, eosinophiles 4, lymphocytes 67, monocytes 3, myelocytes 1.

She was given intravenously 5 mg. of methylene blue dissolved in 5 c.c. of water, added to 20 c.c. of a 20 per cent glucose solution. The injection lasted fifteen minutes. One-half hour after the end of this injection, the tint of the skin, as well as the respiration and the pulse rate, returned to normal. The venous blood, which had then a normal color, contained no further methemoglobin. The white blood cell count was 13,800. She drank eagerly three bottles during the course of the night.

The child was discharged the next day.

Five days later, the patient was hurried again to the clinic. She had been quite normal at home, taking her feedings, having normal stools and normal color. During the preceding night she had cried a great deal and the mother had the impression that cyanosis was recurring. At daybreak she saw that the skin appeared as blue as it had during the former spell. By the time the child was seen she was in the seventh hour of the attack. The general condition being really alarming, caffeine was administered. An attempt was made to give methylene blue intravenously, but just as the injection was started, the patient died.

The blood removed just before the child's death was again found to contain large amounts of methemoglobin and about 100 gammas per 100 c.c. of nitrites.

*Autopsy Report* (Dr. J. Picard).—Good nutrition. Small intestine: normal. Colon: Throughout the sigmoid and in part of the rectum was found a large hemorrhagic, confluent ulceration with marked thickening of the intestinal wall. Spleen: normal volume, chocolate-like color. (This was the only evident sign of methemoglobinemia.) The other organs seemed to be normal.

*Microscopic data:* Spleen: Normal red and white pulp. In the red pulp numerous deposits of brown blood pigment. Liver: A few exudative foci scattered in the parenchyma, containing chiefly mononuclears. Kidneys: Normal. Colon: Ulceration of the mucosa, with marked congestion and interstitial hemorrhages in the submucous layer. The muscular layers appear to be normal.

The benzedrine reaction was positive in fecal material recovered from the colon and negative for that contained in the small intestine. Stool cultures were negative for nitrosobacillus. The well containing the water used for the dilution of the formula was two meters away from the cesspool.

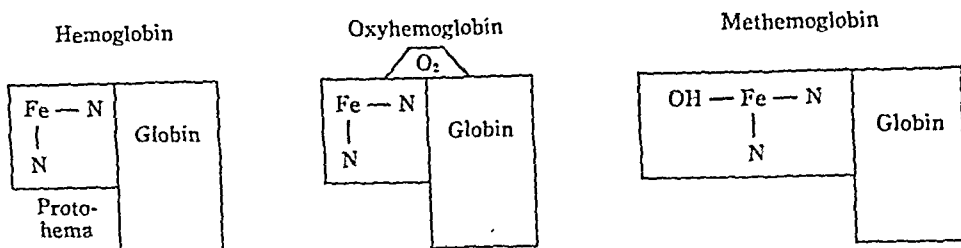
This water contained 180 mg. nitrate per liter, and traces of nitrite. The bacteriologic examination of this water revealed the presence of a few colibacilli.

No other members of the family appeared to suffer from the use of this water.

## DISCUSSION

In the two cases recorded herein, diagnoses of bronchopneumonia, infantile cholera, and congenital malformation of the heart were ruled out, and the cyanosis was attributed to methemoglobinemia.

Methemoglobin<sup>2</sup> is an hydroxide of hemoglobin, in which the OH group is directly bound to the trivalent iron.



Several agents have the capacity of transforming, in vitro and in vivo, hemoglobin into methemoglobin (see further).

Methemoglobin is not toxic but is unable to transport oxygen. When two-thirds of the hemoglobin of a dog has been transformed into methemoglobin, the dog dies.<sup>3</sup> After the formation of methemoglobin, if the toxic agent is withdrawn, spontaneous transformation of the methemoglobin into normal hemoglobin occurs.<sup>1</sup> This transformation is almost complete after thirty-six hours.<sup>3</sup> In the first hours after death, a part of the hemoglobin is converted into methemoglobin. Recent work has shown that methemoglobin is a normal constituent of human blood in the proportion of 1 per cent.<sup>3a</sup>

From the clinical point of view, methemoglobinemias can be classified in two groups:

1. *The first group* includes the plasma methemoglobinemias. Here there is no methemoglobin in the red blood cells. But after hemolysis of a part of the red blood cells, the hemoglobin of the corpuscles dissolves in the plasma and is transformed into methemoglobin. It can occur in eclampsia, in blackwater fever, in paroxysmal hemoglobinuria, in sepsis due to anaerobic organisms, in Winckel's disease and others. The latter disease has several synonyms: cyanosis afebrilis icterica, maladie bronzée hématurique de Parrot, etc. It occurs by epidemics in newborn infants of six to thirty days and is characterized by cyanosis, icterus, hemolysis, and methemoglobinuria.<sup>4-8</sup> The methemoglobin of our patients was present exclusively in the cellular elements. Therefore, their disease cannot be classified in this first group.

2. *The second group* includes the cellular methemoglobinemias. When no toxic agent can be detected, one speaks of enterogenic or idiopathic cyanosis. This disease was first described by Stokvis<sup>9</sup> and by Talma<sup>10</sup> in 1902. The cyanosis is slowly progressive and the patient has only digestive troubles: chronic diarrhea or constipation, with or without abdominal pain. Hymans van den Bergh<sup>11</sup> has shown that the blood of several patients with this disease contained nitrites. Other workers<sup>12</sup> found nitrosobacilli in the stools and saliva of the patients.

Included among the toxic agents able to induce methemoglobinemia are the sulfonamides, aniline, nitrobenzenes, acetanilide, nitrites, bismuth subnitrate, potassium chlorate.

In the literature of the subject, the first case reported in an infant was published in 1940 by Schwartz and Rector.<sup>13</sup> Their patient was a girl 2 weeks old, whose familial history was not contributory. She lived in the country and was fed with a formula made with powdered milk. At 9 days of age the parents observed that the child had become deeply cyanotic. After three days, without any treatment, the color of the skin gradually became normal except during crying. On the fifteenth day of life her skin became rapidly cyanotic, and she was rushed to the hospital. Physical examination gave negative results except for the highly abnormal color of the skin. The white blood cell count was 30,000 and the blood contained 57 per cent methemoglobin. Three mg. of methylene blue per kilogram of body weight were administered intravenously. In one-half hour the cyanosis had completely disappeared. Following this episode there was no recurrence of symptoms. Nitrosobacilli in the stools, nitrites in the blood, and nitrates in the water used for dilution of the powdered milk were not sought. The authors did not report whether or not the formula was changed after the stay of the child in the clinic.

In 1945, Comly<sup>14</sup> discovered the etiologic process. In his paper he presented two of his own cases and discussed several others, similar in nature, verbally communicated to him by other physicians. The following conclusions were made by Comly:

1. The disease occurs in infants of less than 2 months.

2. These children live in the country and are fed powdered milk diluted in well water. The well water employed in the children's diet contains nonpathogenic microbes, significant amounts of nitrates and small amounts of nitrites:

In his first case	619 mg. ion $\text{NO}_3$ per liter
	0.4 mg. ion $\text{NO}_2$ per liter
In his second case	388 mg. ion $\text{NO}_3$ per liter
	1.3 mg. ion $\text{NO}_2$ per liter

3. The first patient had three attacks of methemoglobinemia followed by complete recovery after withdrawal of the well water from the formula.

4. The adults drinking the same water were not sick and their blood contained no pathologic amounts of methemoglobin. The amount of water that they drank was relatively much less than for the infants.

5. Each attack of methemoglobinemia was completely cured with methylene blue.

Unfortunately he did not look for nitrites in the blood of the patients during the attacks.

The following question is now in order: are relatively small amounts of nitrates responsible for such accidents? Let us compare all those patients' histories with the fatal attacks of methemoglobinemia occurring after administration of bismuth subnitrate by roentgenologists, in administering contrast media,

or by physicians as a therapeutic agent for enteritis. The following cases are reported by Roe:<sup>15</sup>

1. An infant, 1 month of age, had been receiving bismuth subnitrate for a refractory enteritis. After twenty-four hours of treatment, in which 7 Gm. of the drug had been given, a marked cyanosis appeared. After forty-eight hours, the child was strangely cyanosed. The drug was then stopped. By this time the child had taken 13 Gm. of bismuth subnitrate. He died twenty-four hours later with cyanosis and hypothermia. At post-mortem no characteristic lesion was found. Blood analysis showed that the cyanosis was due to corpuscular methemoglobinemia.

2. An infant, 3 weeks old, suffering from enteritis, had been given 3 Gm. of bismuth subnitrate by gavage for x-ray purposes. The child died twelve hours later, with strong cyanosis due to methemoglobinemia.

The other cases of Roe will not be discussed because of lack of laboratory data.

It is obvious that the toxic element was the  $\text{NO}_3$  ion, for such accidents have never been reported after administration of another bismuth salt.

In Table I the amount of  $\text{NO}_3$  ion absorbed by our patients and by the patients of Comly is converted into the corresponding amount of bismuth subnitrate, and compared to the amount of the drug ingested by the patients reported by Roe.

TABLE I

REPORTED BY	CASE	AGE	MG. IONS $\text{NO}_3/\text{l}$	CORRESPONDING AMOUNT OF BISMUTH-SUBNITRATE		DIARRHEA
				TOTAL AMOUNT (GM.)	AMOUNT (GM.) PER DAY	
Ferrant	1	1 mo.	497	30	1.5 during 21 days	+
	2	1 mo.	180	14	0.5 during 21 days	-
					0.6 during 6 days	Ulceration of the sigmoid colon
Comly	1	1 mo.	619	19	2.7 during 2 days	-
					2.7 during 2 days	-
					2.7 during 2 days	-
	2	1 mo.	388	35	1.1 during 30 days	+
<i>Cases of Fatal Intoxication With Bismuth Subnitrate</i>						
Roe	1	1 mo.		13	6.5 during 2 days	+
	2	3 weeks		3	3.0 during 1 day	+

In accordance with the similarity observed in Table I, it seems logical to conclude that the methemoglobinemia of our patients and of the patients of Comly was due to the nitrates in the well water. Similar amounts of  $\text{NO}_3$  ion from bismuth subnitrate introduced into the intestinal tract of infants with diarrhea induced fatal attacks of methemoglobinemia. In our second case there was no diarrhea, but at post-mortem a large ulceration of the sigmoid colon was unexpectedly found. It is possible that the same lesion occurred in the second patient of Comly.



The *mechanism* of the toxic action of the  $\text{NO}_3$  ion will now be discussed.

Normally, during digestion, nitrates are produced in the intestinal tract. These are not absorbed but are reduced to nitrites and then to ammonia. When relatively large amounts of nitrates are ingested by a child suffering from accelerated intestinal transit and inflammation of the mucosa, it is possible that the nitrites have no time to be completely reduced and that, through this defective mucosa, they are able to reach the circulating blood. Nitrites are catalytic agents. It is quite abnormal to find them in the blood. It remains to be proved by dog experimentation whether amounts of nitrites of about 100 gammas per 100 c.c. are able to induce abrupt attacks of methemoglobinemia.

There are other evidences to sustain this pathogenic hypothesis.

1. In idiopathic cyanosis there are digestive disorders and Hyman and van den Bergh found nitrites in the blood of a few patients.

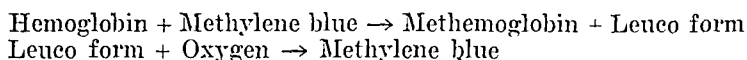
2. The digestive mucosa of the child is normally more delicate than that of the adult.

3. In infants the metabolism of fluids is more rapid and more important.

4. The nitrates are introduced in the ingested water, which is polluted by potentially pathogenic microorganisms.

The former *treatment* of the methemoglobinemias consisted of blood withdrawal and transfusion, oxygen therapy, and rest of the gastrointestinal tract.

The use of methylene blue represents a successful innovation.<sup>16</sup> Methylene blue, which is a very efficient reducing agent, increases the combustion of oxygen by the human erythrocyte some twenty to thirty times. On the other hand, methylene blue is considered to be the antidote of hydrocyanic acid.<sup>17</sup> Favorable results have also been claimed for methylene blue in the treatment of sulfhemoglobinemia.<sup>18-21</sup> Its beneficial action in carbon monoxide intoxication is questioned by many.<sup>22</sup> The clinically active dose is 1 to 2 mg. per kilogram of body weight. When rapid action is desired, it may be administered intravenously. In chronic cases it is given by mouth. Some authors object to the use of methylene blue in that it has the property of transforming, *in vitro*, hemoglobin into methemoglobin. Methylene blue itself is transformed into the leuco form, which in turn reacts with oxygen and forms again methylene blue.



At first sight it seems illogical to administer a methemoglobin-forming agent to patients suffering from methemoglobinemia. But clinical experience forces us to accept what biologists are unable to explain. Several theories have been proposed, none of which can be regarded as conclusive.

Other harmful effects of methylene blue have been pointed out: anxiety, obsession, paresthesias, depressing action on respiratory and circulatory centers. But to obtain such untoward symptoms one must inject amounts far greater than those usually administered. Brooks<sup>23</sup> advises that methylene blue be dissolved in hypertonic glucose solution because *in vitro* glucose transforms methemoglobin into oxyhemoglobin. Ascorbic acid and niacin possess the same property.

Lederer<sup>24</sup> advises the replacement of methylene blue by thionine, a violet dye, not toxic and not methemoglobin formative, which has a reducing power five times greater than that of methylene blue. Hausechild<sup>25</sup> used methylene blue and thionine with comparable results. In our cases, thionine was not employed because it was unobtainable.

#### CONCLUSIONS

The incomplete modernization of rural districts frequently makes it necessary for the inhabitants to resort to the use of well water containing excessive amounts of nitrates for the diluting of powdered milk feedings. These nitrates are probably considerably more toxic for newborn infants than for adults, especially if the infants have a digestive disorder.

It is probable that nitrates are transformed in the intestinal tract into nitrites, which in turn are resorbed and act in the blood stream as a methemoglobin-forming agent.

The outstanding feature in the clinical picture is the contrast between the cyanosis and the alarming condition of the patient on the one hand, and the normal aspect of the respiratory and circulatory system, on the other. The anoxemia, which results from the high level of methemoglobin in the blood, explains the shock, polypnea, dyspnea, tachycardia, and prostration. Diarrhea may be present. The color of the blood varies from brown red to brown black. There is no hemolysis and the methemoglobin is corpuscular. On the average, the methemoglobin level in the blood seems to be above 50 per cent of the total pigment. The white blood cell count during attacks is elevated.

In our second case, blood drawn during the attack contained about 100 gammas of nitrite per 100 c.c. We strongly suggest similar investigations in related cases.

At autopsy in the second case, large ulcerations of the mucosa of the sigmoid colon were found. The other organs appeared to be normal.

Treatment must be instituted quickly. The toxic agent must be immediately withdrawn, and transfusions are certainly in order. However, methylene blue (1 or 2 mg. per kilogram of body weight) is effective and seems to be free from risk.

The prophylaxis of such accidents is the concern of the Public Health Department.

#### SUMMARY

Two cases of methemoglobinemia in newborn infants are presented. They appeared to be caused by nitrates in the well water used for the dilution of powdered milk in the formula.

In the first case, the acute stage was successfully treated with transfusions.

In the second case, the first attack was healed by methylene blue. However, treatment was begun too late to save the patient in a second attack.

The literature of the subject is briefly reviewed.

The pathogenesis of the disease is discussed in connection with the finding of large amounts of nitrates in the well water and of small amounts of nitrites in the blood of the second patient.

We thank Professor Louis Maldague for permission to publish the cases from his service. We also thank Mr. Jules Ladenheim for help in the translation. We are indebted to Mr. J. Steenhoudt, who made the chemical and spectroscopic analyses, to Dr. Piet de Somer for bacteriologic determinations and to Dr. Joseph Picard for the pathologic data.

## REFERENCES

1. Halpern et Dubost: *Bull. Soc. Chim. Biol.* 21: 717, 1939.
2. Florkin: *Biochimie humaine*. Liège, 1940.
3. Roche, J.: *Arch. internat. de Pharmacodyn. et de thérap.* 37: 358, 1930.  
a. Paul, W. D., and Kemp, C. R.: *Proc. Soc. Exper. Biol. and Med.* 56: 55, 1944.
4. Feldmann, W. M.: *Brit. J. Child. Dis.* 24: 113, 1927.
5. Finkelstein: *Säuglingskrankheiten*, ed. 3, Amsterdam, Elsevir, p. 378.
6. Laffont: *Encycl. méd. chir. Pédiatrie*, p. 4083.
7. Nobécourt et Babonneix: *Traité de médecine des enfants* 2: 22; 4: 95.
8. Cornelia de Lange, and associates: *Ziektenleer van den Pasgeborene*, Amsterdam, 1944, p. 34.
9. Stokvis: *Nederl. Tijdschr. v. Geneesk.* Oct. 12, 1902.
10. Talma: *Nederl. Tijdschr. v. Geneesk.* Oct. 4, 1902.
11. Hymans van den Bergh, A. A.: *Deutsches Arch. f. klin. Med.* 83: 86, 1905.
12. Mackenzie and Wallis: *Quart. J. Med.* 7: 73, 1913.
13. Schwartz, A. S., and Rector, E. J.: *Am. J. Dis. Child.* 60: 652, 1940.
14. Comly, H. H.: *J. A. M. A.* 129: 112, 1945.
15. Roe, H. E.: *J. A. M. A.* 101: 352, 1933.
16. Lederer, J. A.: *Le Scalpel* 90: 366, 1937.
17. Hanzlik, P. J.: *J. A. M. A.* 100: 357, 1933.
18. Williams, J. R., and Challis, F. E.: *J. Lab. and Clin. Med.* 19: 166, 1933.
19. Wendel, W. B.: *J. Clin. Investigation* 18: 179, 1939.
20. Geiger, J. C.: *J. A. M. A.* 100: 1103, 1933.
21. Binet: *Presse Méd.* 83: 1500, 1939.
22. Haggard, H. W., and Greenberg, L. A.: *J. A. M. A.* 100: 2001, 1933.
23. Brooks, M. M.: *Am. J. Physiol.* 114: 160, 1935.
24. Lederer, J. A.: *Arch. Internat. de Pharmacodyn. et de thérap.* 55: 357, 1937.
25. Hauschild, F.: *Klin. Wchnschr.* 18: 1580, 1939.

# METHEMOGLOBINEMIA OCCURRING IN INFANTS FED MILK DILUTED WITH WELL WATER OF HIGH NITRATE CONTENT

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THIS report concerns two newborn infants with proved methemoglobinemia successfully treated with injections of methylene blue and a third infant who probably had methemoglobinemia and recovered spontaneously. The methemoglobinemia in all three of the infants was associated with the ingestion of milk mixtures diluted with well water containing a large amount of nitrate ions.

Our attention was directed to these observations by a recent article by Comly<sup>1</sup> describing the occurrence of methemoglobinemia in several infants in Iowa under similar circumstances. He has hypothesized that the ingested nitrate is reduced to nitrite by the intestinal flora and that the absorbed nitrite then changes hemoglobin to methemoglobin. Irrespective of whether or not Comly's theory is correct, the facts regarding the ingestion of milk mixtures diluted with well water of high nitrate content are uniformly present both in his series of infants and in ours.

## REPORT OF CASES

CASE 1.—J. K., white male infant, 4 weeks of age, was admitted to the University of Kansas Hospitals at 10 A.M., Dec. 30, 1945, from Louisburg, Kan., because of cyanosis and drowsiness. The infant was the firstborn of twins who were delivered after a pregnancy of eight months. The birth weight was 5 pounds, 8 ounces. After delivery he was resuscitated with some difficulty. At the age of 3 days he was placed on a dilute milk-mixture containing 10 ounces of evaporated milk and 20 ounces of boiled water with 5 per cent carbohydrate added. Three ounces were offered every four hours. He remained in the hospital for thirteen days and is said to have become cyanotic when he cried during this time. After he left the hospital, the cyanosis increased in frequency and severity, and was constantly observed to be present by the time he was 3 weeks old. He became progressively more lethargic and listless, and at 3 A.M. on the day of admission he became very deeply cyanosed and very listless. The intensity of the cyanosis had diminished before admission, but the infant was still very lethargic and cyanotic when the decision was made to bring him to the hospital.

Physical examination revealed a poorly nourished infant weighing 2,525 Gm. with a peculiar bluish gray discoloration that was not typical of true cyanosis. The fontanel did not bulge, the neck was not stiff, there was no lymphadenopathy and the pharynx was normal. The breath sounds were normal and equal on both sides. No râles were heard. The respiratory rate was 60 per minute. No dullness to percussion could be made out over the lung fields. The heart was not enlarged. There was a soft systolic murmur which was heard best at the apex. No thrills or arrhythmia were noted. The heart rate was 132 per minute. The examination of the abdomen, genitals, and extremities was entirely negative. The infant was given oxygen by nasal tube, but no improvement in the cyanosis was noted.

Methemoglobin and hemoglobin concentrations were determined by the method of Evelyn and Malloy.<sup>2</sup> When the blood was drawn for these determinations, it was markedly chocolate in color. The methemoglobin concentration was 6.7 Gm. per 100 c.c. of whole blood.

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The hemoglobin concentration was 11.5 Gm. per 100 c.c. of whole blood. This left only 4.5 Gm. of functioning hemoglobin per 100 c.c. of whole blood. Five tenths cubic centimeter of 1 per cent methylene blue was given intravenously and within one half hour the baby's color was normal, respirations were 30 per minute and he was clinically well. The methemoglobin concentration in the blood one half hour after the administration of the methylene blue was 0.4 Gm. per 100 c.c. of whole blood.

Further laboratory work showed the urine to be negative. The red blood cell count was 4,260,000 per cubic millimeter. The white blood cell count was 22,700 per cubic millimeter. The differential white blood cell count was normal. Roentgenograms of the chest showed the lungs to be clear and the heart to be normal in size and shape.

Two days later the infant had mild generalized clonic convulsions. The nonprotein nitrogen was 36.6 mg. per cent; the calcium was 10.9 mg. per cent and the blood sugar was 91 mg. per cent at this time. These convulsions became less and less severe and after three days stopped altogether. It was thought that these were probably due to cerebral anoxemia associated with the low amount of functional hemoglobin found on admission. At the time of discharge eight days after admission, the baby weighed 2,815 Gm.; he had a normal color and showed normal activity.

CASE 2.—J. K., female twin sibling of J. K. (Case 1), was born four hours after her brother. She was admitted to the University of Kansas Hospitals at 2 P.M. on Dec. 30, 1945, with the same complaints as her twin brother.

At birth this infant had weighed 7 pounds and 5 ounces and had always been stronger than her sibling, but on numerous occasions she had, since dismissal from the hospital where she was born, become cyanotic around the lips. She had had slight episodes of listlessness, but on the day before admission she became very cyanotic and lethargic. Since the third day of life she had been offered every four hours 3 ounces of a milk mixture containing 10 ounces of evaporated milk, 20 ounces of water and 1 ounce of syrup.

Physical examination on admission showed a lethargic but not comatose infant weighing 3,220 Gm. The skin had the same peculiar bluish gray discoloration as that of her twin and was not relieved by oxygen inhalations. The respiratory rate was 64 per minute. The pulse rate was 168 per minute. The physical examination otherwise was entirely negative.

Laboratory examination showed a total hemoglobin of 13.5 Gm. per 100 c.c. of whole blood and a methemoglobin concentration of 9.6 Gm. per 100 c.c. of whole blood, leaving 4.3 Gm. of functioning hemoglobin per 100 c.c. of whole blood. The blood was the same pronounced chocolate color as noted in Case 1.

The infant was given 0.6 c.c. of 1 per cent methylene blue intravenously. Twenty minutes later the baby's color had become normal, the respiratory rate had dropped to 40 per minute and the pulse rate was 130 per minute. One half hour after the methylene blue was given, the methemoglobin concentration was 0.7 Gm. per 100 c.c. of whole blood.

The infant seemed perfectly well thereafter and was dismissed on the eighth hospital day weighing 3,375 Gm.

The water used in making the milk mixtures for this set of twins was obtained from a well dug on the premises. Chemical analysis by the Division of Public Health Laboratories of the Kansas State Board of Health showed that the well water contained 70 mg. of nitrate nitrogen and only a trace of nitrite nitrogen per liter.

CASE 3.—A third infant, F. K., was admitted to the University of Kansas Hospitals from Greely, Kan., on July 25, 1945, because of cyanosis, which in retrospect we believe was the result of an excessive methemoglobinemia.

This infant was 2 weeks old when admitted. Five days before admission this infant became blue, and when he cried the cyanosis was greatly exaggerated. There was no respiratory embarrassment and the baby continued to eat and sleep well. The bluish discoloration continued until admission. This infant was born at home and weighed 8 pounds and 8 ounces at birth. He never was breast fed but was given a milk mixture containing one part Similac and two parts of boiled water. He also was given water between feedings.

Physical examination showed an active infant weighing 3,550 Gm. The skin was bluish gray in color. There was no dyspnea or tachypnea. The pulse rate was rapid. There was no cardiac enlargement and no thrills. A faint systolic murmur was heard over the pulmonary area. The lungs were clear to auscultation and percussion and the rate was not abnormally rapid. The liver was palpable 4 fingerbreadths below the right costal margin. The remainder of the physical examination was entirely negative.

Laboratory examination showed the urine to be negative. The red blood cell count was 4,880,000 per cubic millimeter. The white blood cell count was 10,700 per cubic millimeter with a normal differential. There was 13.5 Gm. of hemoglobin per 100 c.c. of whole blood. Methemoglobin determinations were not made. The calcium level was 12.1 Mg. per cent. Roentgenograms of the chest showed the lungs to be clear and the heart normal in size and shape.

Oxygen was administered but it did not decrease the cyano-sis and hence was discontinued. The cyanosis gradually diminished and by the end of the first week in the hospital it had disappeared completely. The patient was discharged on the eighth hospital day apparently entirely well.

Water was obtained from the well used by the family and was tested by the Division of Public Health Laboratories of the Kansas State Board of Health. The water was found to contain 300 mg. of nitrate nitrogen and a trace of nitrite nitrogen per liter.

#### COMMENT

The methemoglobin concentrations in the blood of the twins in this report were much higher than those found by Comly in the group of infants in Iowa. The higher concentrations obtained in the twins reported here probably were the result of an earlier recognition of the condition. In Comly's series the infants remained in the hospital several days before methemoglobin determinations were done, thus permitting a certain amount of spontaneous recovery to occur. The concentration of methemoglobin in the blood probably diminishes rapidly in a period of four or five days if the infants are fed milk mixtures that are free of nitrates. The infant in the present report on whom determinations were not made for methemoglobin probably is an example of the spontaneous cure that can result if the infant is placed on undiluted cow's milk.

Death has been reported as a result of severe methemoglobinemia. It seems possible that these infants might have had a fatal outcome if further reduction of functional hemoglobin had occurred. It is surprising that they could have survived with their functional hemoglobin reduced to as low as 4.3 Gm. per cent.

The amount of nitrate ingested in relation to body weight apparently is the determining factor as to whether clinical methemoglobinemia develops or not. All adults drinking water from the well supplying the twins reported here were tested for methemoglobinemia and none was found. A 6-month-old infant, who lived in the same house and who has been fed a milk mixture made with the same water since birth, has never exhibited any signs of methemoglobinemia. However, his formula was made with equal parts of whole cow's milk and boiled water. For this reason his ingestion of nitrate ion has probably been proportionately less. For this reason it would seem wise to feed infants living on farms, when the character of the water is unknown, milk mixtures which are fairly concentrated or made with water obtained from a source known to be satisfactory.

The use of methylene blue in the treatment of this condition has been well reviewed by Comly; in our cases its effect was dramatic and left nothing to be desired.

The geographical distribution of cases of methemoglobinemia associated with the ingestion of well water containing large amounts of nitrate ions has been extended to include Kansas as well as Iowa. It is likely that the location and condition of wells dug in many rural areas in other states are such as to permit the contamination of the water by seepage from barnyards and other sources high in nitrogenous materials. If such is the case, it would be expected that methemoglobinemia might be encountered over wider areas than has yet been reported, particularly since the feeding of milk mixtures and products requiring relatively large amounts of water is probably widespread.

Methemoglobinemia in newborn infants as the result of absorption of aniline dye from newly stamped and unlaundered diapers has been reported.<sup>3</sup> Consequently it is important to bear in mind that the ingestion of contaminated well water is not the only factor which can produce methemoglobinemia in this age group.

#### SUMMARY

1. Two cases of proved methemoglobinemia in newborn infants probably caused by the ingestion of water with a high concentration of nitrate ion are reported. A third case of suspected methemoglobinemia from the same cause is also added.

2. The efficacy of methylene blue in the treatment of this condition is corroborated.

3. It is suggested that special precautions be taken in rural areas to see that any water used in the feeding of infants is safe in respect to its nitrate content.

#### REFERENCES

1. Comly, H. H.: *J. A. M. A.* 129: 112, 1945.
2. Evelyn, K. A., and Malloy, H. T.: *J. Biol. Chem.* 126: 655, 1938.
3. Graubarth, J., Bloom, C. J., Coleman, F. C., and Solomon, H. N.: *J. A. M. A.* 128: 1155, 1945.

# THE DIAGNOSIS OF ABORTIVE POLIOMYELITIS

## A STUDY OF ILLNESSES OCCURRING IN 1,123 CONTACTS OF PATIENTS WITH POLIOMYELITIS

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IN THE older writings on poliomyelitis, the essential criterion for making a diagnosis was the finding of flaccid paralysis in one or more muscle groups. However, since the classical studies of Wickman<sup>1</sup> it has been evident that in addition to paralytic cases, there are also individuals who pass through the acute early symptoms of the disease but never progress to the point of muscle paralysis. These have been called nonparalytic or abortive cases. Patients with this form of the disease may show signs of meningeal irritation and changes in the spinal fluid similar to those of the paralytic cases, but the course is likely to be milder and of shorter duration. At the present time, most physicians are able to recognize nonparalytic cases and to care for them adequately from the public health viewpoint. Unfortunately, the problems of diagnosis and control involve a far larger number of individuals than are represented by the paralytic and the diagnosed nonparalytic cases. Until the extent of dissemination of the virus in a community is better known, and until the nature of the mild symptoms caused by the infection is more widely appreciated, measures directed toward the control of epidemics can be of little value.

It is an almost universal observation of physicians who have worked intimately with an epidemic of poliomyelitis that during such a period many individuals are ill with clinical symptoms of an entirely nonspecific nature but which appear to be related in some way to the epidemic itself. The closeness of the association between such individuals and recognized paralytic cases may suggest that the etiologic agent is the same. On the other hand, the clinical picture shows nothing on which to base the diagnoses. Even the findings in the spinal fluid are not necessarily characteristic, for although an increase in the number of cells is occasionally found, this is unusual and not the expected result. Furthermore, studies of the distribution of the virus at the time of an outbreak of the disease have shown many individuals to be infected who had only mild and brief symptoms, or even none at all.<sup>2</sup> In the absence of more exact methods for making a diagnosis of infection with the virus of poliomyelitis, the problems facing the practicing physician are difficult and confusing. On the one hand, if he makes the diagnosis only on the basis of paralysis or changes in the spinal fluid, a large number of individuals will be circulating in the community and spreading the virus among their intimate friends. On the other hand, to label every minor or suspicious illness as a case of poliomyelitis may arouse unjustifiable alarm in the family and community. Until the time arrives when confirmation of a suspected diagnosis can be quickly and accurately obtained

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by laboratory procedures, the physician must rely on his own experience and judgment, and no uniform policy can be expected.

As an aid to the recognition of early and mild cases of the disease, it seems necessary to obtain a clear picture of the clinical symptoms which might be expected. Although numerous reports have pointed out the general characteristics of "abortive poliomyelitis,"<sup>2</sup> the studies carried out during the 1944 outbreak in the Buffalo, N. Y., area, offered an unusual opportunity to amplify and extend the information.

#### STUDY MATERIAL

As part of an epidemiological study of the reported cases of poliomyelitis in the Buffalo, N. Y., area, during the summer of 1944, detailed investigations of activities and contacts were made in approximately 900 cases. The methods of investigation have been described elsewhere.<sup>3</sup> In 194 of these individuals, the epidemiological data obtained were too inadequate to be used. However, in 504 instances, one or more individuals with whom the patient had been in close contact had been ill during the general period of the patient's disease, with symptoms which had not been diagnosed as poliomyelitis. In some, this illness had occurred from one to three weeks before the onset of the poliomyelitis and could have been a possible source of the virus; in others, it occurred simultaneously, suggesting a common source; and in still others, it occurred from one to three weeks afterward and was interpreted as a secondary illness probably acquired by contact. Whenever possible, the descriptions of these illnesses were amplified by visits to the homes concerned. The actual number of associated illnesses, including twenty-nine cases of poliomyelitis, was considerably larger than that finally used in the study. Many, however, were excluded because of uncertainties regarding the closeness of the contact. There remained 1,123 instances in which circumstances pointed to the likelihood of the associated illnesses being caused by the same agent which was responsible for the patients' diagnosed poliomyelitis. The following report is based on an analysis of these associated illnesses.

This group of illnesses was selected for study because, on circumstantial evidence, they would be assumed to be caused by the virus of poliomyelitis regardless of the symptoms presented. Such an assumption is, of course, open to the criticism that no positive proof can be offered that every illness was actually caused by the virus. However, in selecting the illnesses from the information at hand, care was used to exclude any in which the contact with the paralytic case was either vague or indirect. Furthermore, as shown in Tables I and II, approximately 50 per cent of the individuals with minor illnesses were members of the immediate family of poliomyelitis patients—parents, siblings, and grandparents. Playmates, friends, and neighbors comprised an additional 40 per cent. The remaining 10 per cent was made up of aunts, uncles, cousins, and other relatives. The closeness of the relationship to the patient added to the probability of a common infectious agent being responsible for all. While not necessarily conclusive, the circumstantial evidence points strongly toward the poliomyelitic nature of the illnesses of these individuals.

## RESULTS

The types of illnesses encountered among the group varied widely. In some instances, another case of the disease was diagnosed. Others were sick with fever, vomiting, headache, and painful extremities, symptoms which persisted for a week or longer and were followed by a prolonged period of convalescence. Such illnesses are suggestive of undiagnosed nonparalytic poliomyelitis. In still others, the only symptom consisted of a running nose, a day

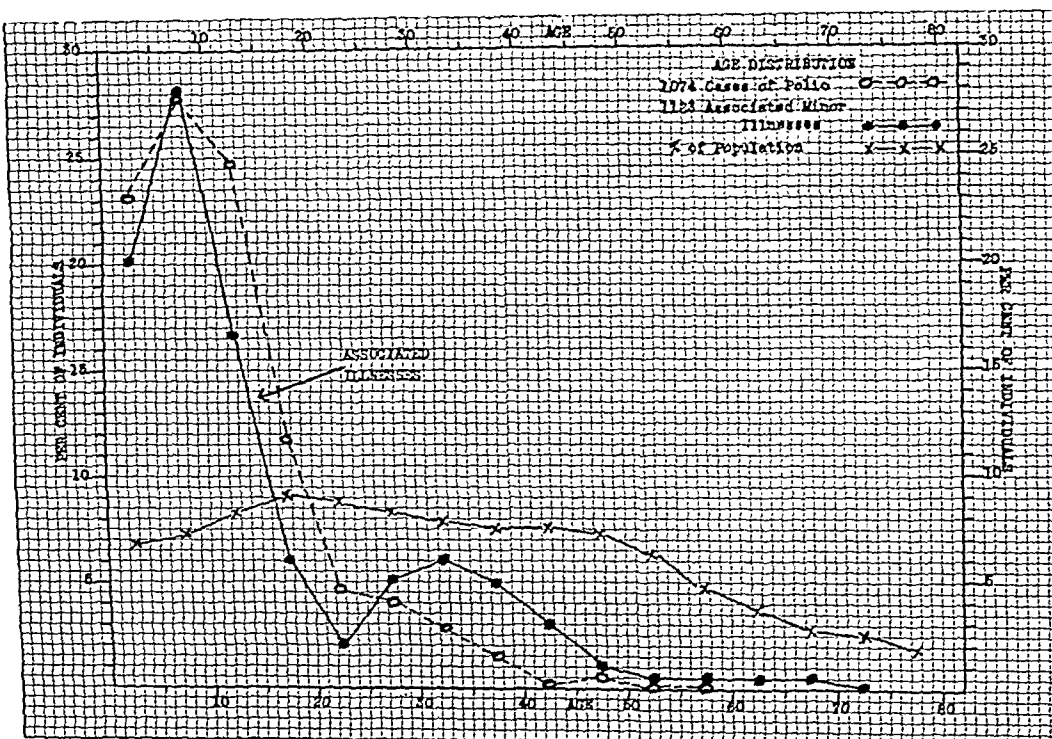


Fig. 1.—Age distribution curves of 1,074 reported cases of Poliomyelitis, 1,123 associated minor illnesses, and of the general population.

of indisposition, a sore throat, or a period of nausea and vomiting. Except for the group which showed meningeal or paralytic symptoms, the descriptions rarely contained any criteria from which a distinction could be made between a

TABLE I. RELATIONSHIP OF INDIVIDUALS HAVING MINOR ILLNESSES TO POLIOMYELITIS PATIENTS

RELATIONSHIP	NUMBER IN IMMEDIATE FAMILY	TOTAL NUMBER OF ILLNESSES	PERCENTAGE
Parents	197		
Siblings	342		
Grandparents	13		
Neighbors, friends or playmates		552	49
Cousins, aunts, uncles		445	40
Others		114	10
Total		12	1
		1,123	100

TABLE II. NATURE OF THE CONTACT BETWEEN DIAGNOSED CASES OF POLIOMYELITIS AND 1,123 INDIVIDUALS WHO HAD MINOR ILLNESSES

NATURE OF CONTACT	NUMBER	PERCENTAGE
Household	559	50
Neighborhood	408	36
Casual	156	14
Total	1,123	100

mild poliomyelitic infection and one caused by common pathogens. Several illustrations may help to visualize the type of illnesses encountered.

EXAMPLE I.—About August 1, a playmate of the patient had a sore throat, “cold,” and fever which were thought by the family to represent a “mild case of infantile paralysis.” The patient, an 8-year-old boy, developed poliomyelitis of the bulbar type with indefinite symptoms beginning on August 10, throat paralysis on August 12, and death four days later. On August 21 and 22, three of the patient’s siblings, aged 3, 5, and 12 years, were ill with fever and vomiting. In one of these, mild weakness in the muscles of one leg was discovered several weeks later. On August 25, another sibling of 6 years had a similar episode of fever and vomiting. The mother, who had been away from home from August 5 to 16, returned on this latter date to care for the patient. On August 30, she complained of a sort throat, headache, and pains in the legs which persisted for several days. All four members of a neighboring family were also ill with fever and vomiting at about the same time, although no definite dates could be established.

In this group, gastrointestinal symptoms seemed to predominate, but three individuals had other symptoms which suggested true poliomyelitis in a mild and nonparalytic form.

EXAMPLE II.—During the epidemic this family was so apprehensive that the members left town and spent the summer with relatives 200 miles away. They returned on September 18 to a neighborhood in which there had been several cases of poliomyelitis and many minor and apparently nonspecific illnesses. Upon arrived, the 11-year-old girl in the family was greeted by neighbors, aged 3 and 5 years, both of whom had profuse nasal discharges called “colds.” On September 28, ten days after this contact, the 11-year-old child developed a watery nasal discharge and a little pain in head and eyes. However, she continued to play actively until October 2, when acute meningeal symptoms developed and the clinical diagnosis of poliomyelitis was confirmed by lumbar puncture.

The patient was in the habit of hugging and kissing her two smaller siblings each day. On October 12, fourteen days after the oldest child first developed symptoms, both younger ones had a “nose cold” with watery discharge which lasted from one to two days and subsided without complications.

Rhinitis was apparently the leading symptom in this group.

EXAMPLE III.—This family with eight children lived in a rural village in which several cases of poliomyelitis developed at a time when minor illnesses were prevalent. The father worked beside a man whose wife had poliomyelitis beginning on July 4, but neither man admitted symptoms of any kind. On August 8, the 14-year-old child complained of nausea and sore throat which lasted two days. On the following day, the 4-year-old child acted sick and had no specific symptoms, but ten days later he complained of sore legs and limped for a time. On August 13, a 7-year-old child complained of nausea, headache, and a slight fever for two days. Another child of 2 years was irritable and refused to eat for the single day of August 16. On August 17, the mother had chills and fever, sore throat, pains in back of the neck and legs, and could not walk comfortably. Two days later she felt well. On August 22, a 10-year-old child had prodromal symptoms of headache and mild fever with acute meningeal symptoms developing on August 27 and progressing to paralytic poliomyelitis. A 12-year-old child had nausea, malaise, and probably fever on August 31

and September 1. The two other children, aged 3 weeks and 6 years, had no symptoms of any kind as far as the parents could recall.

In this family, the mother and six of her eight children were ill within a period of three weeks. Only one of these illnesses was diagnosed as clinical poliomyelitis.

EXAMPLE IV.—During the early phase of the epidemic, several illnesses occurred in boys belonging to a local troop of Boy Scouts. One of these was diagnosed as possible bulbar poliomyelitis on June 26. An intimate friend, aged 12, developed a sore throat on July 3 and felt poorly for several days. On July 4, this latter boy spent the day with his sister, aged 8, and grandfather, aged 65. The sister became acutely ill with a mild bulbar poliomyelitis on July 16, and at the same time the grandfather developed an acute sore throat.

Related to this patient with bulbar poliomyelitis were a brother, aged 13, and a grandfather, aged 65, both of whom had illnesses characterized particularly by symptoms referable to the throat. /

#### SYMPTOMS

In order to obtain a picture of the dominant symptoms of the entire group of 1,123 individuals, these are presented in Table III. Since the descriptions were obtained by interview and not by observation, the terms used correspond in so far as possible to the objective facts stated. Those described as stiff neck and back, headache, nausea and vomiting, sore throat, and diarrhea can be relied upon. The term "cold," however, is less definite in significance, for while it usually designates a respiratory infection involving the nose, among the less educated part of the population it is sometimes used to indicate a sore throat, a "cold in the bowels," fever with aches and pains. Although the terms used in the table are necessarily of limited significance as descriptions of the entire illness, they nevertheless indicate the symptoms which attract attention in average homes and represent the basis from which the practicing physician and health officer must work. The symptoms have been arranged in the order of decreasing suspicion of poliomyelitis. Other symptoms which occurred in combination with those higher in the list were excluded from the counts in the lower part. Thus, although meningeal symptoms, described as stiff neck or back, and pains or weakness of the extremities, were encountered less frequently than others, because these were most suggestive of true poliomyelitis, they were placed first in the table. Headache, which was usually persistent, was placed next. Because of the uncertainty of the significance of the term "fever," this was given a somewhat lower place. A hierarchy of single major symptoms of each individual was thus set up, in which less important symptoms appearing in combinations were relegated to lower positions.

The table demonstrates that a large majority of the individuals lack symptoms that would indicate to a physician a specific involvement of the central nervous system. Thus, in only 19 per cent of the group was there either stiff neck, stiff back, weakness of the extremities, or painful extremities. Usually such symptoms disappeared in from twenty-four to forty-eight hours without sequelae, but occasionally they persisted for from five to seven days. In the great majority—over 80 per cent—the illnesses had no characteristics which could distinguish them from diseases of an entirely different nature. Thus the

nonspecific nature of so many of the symptoms emphasizes the inadequacy of clinical methods for making a diagnosis of infection with the virus of poliomyelitis, and in the absence of a simple confirmatory laboratory test, epidemiological facts may offer helpful guides.

In most instances, more than one symptom was described for each illness, and combinations of all kinds were seen. While fever with nausea and vomiting was encountered most frequently, the combination of fever and sore throat with or without vomiting was also common. The duration of the individual symptoms and of the total illness varied greatly. In many instances they were transient, and the individual felt well within from twenty-four to forty-eight hours. In others, the symptoms persisted for a week with slow convalescence. The clinical picture was in no way consistent, although certain patterns were encountered more frequently than others.

TABLE III. FREQUENCY OF DOMINANT SYMPTOMS OF 1,123 CLOSE CONTACTS OF PATIENTS WITH DIAGNOSED POLIOMYELITIS

SYMPTOMS	NO. OF INDIVIDUALS	PER CENT OF TOTAL
Stiff neck and back	97	9
Extremities weak and painful	111	10
Headache	10	1
Nausea and vomiting	324	29
Sore throat	217	19
Fever	162	14
Other symptoms	202	18
Total	1,123	100

#### COMPARISON WITH EARLY SYMPTOMS OF DIAGNOSED CASES

The term "abortive poliomyelitis," which is in common use, connotes an illness which begins as the true disease but enters the recovery phase before the usual clinical characteristics appear. The minor illnesses which have been discussed should, theoretically at least, be similar to the initial stages of the disease itself. Wilson<sup>4</sup> has tabulated the early symptoms of the disease, but because of the possibility of variation from epidemic to epidemic it seemed desirable in the epidemic under discussion to compare the symptoms encountered among the contact illnesses with both the preparalytic symptoms of individuals who later developed paralysis and with diagnosed nonparalytic cases as well. In all, data from 334 paralytic and 137 nonparalytic cases were studied for comparison with the 1,123 contact illnesses. The results are presented in Table IV.

A similarity between the three groups can be seen in the table. Fever, nausea and vomiting, and sore throat were prominent in all. Meningeal and central nervous system symptoms were, of course, less common among the associated and undiagnosed minor illnesses. In addition, fever was less consistently present among the minor illnesses, which probably indicates nothing more than a milder degree of infection. In other respects the general character and proportion of symptoms in the three groups were similar. It should be pointed out that the differences between the two groups of diagnosed cases may not be significant, since the period of time from which the preparalytic

symptoms were drawn was short in contrast to the entire course of the non-paralytic cases. However, since the diagnostic problem of the physician is difficult only in the absence of paralysis, for the purposes of the present discussion the data as presented in the table seem most pertinent. In general, the facts suggest that the systemic manifestations of infection are similar in the three groups: if the disease fails to progress, evidences of involvement of the central nervous system are minimal

TABLE IV. FREQUENCY OF SYMPTOMS ENCOUNTERED AMONG 1,123 CLOSE CONTACTS OF PATIENTS WITH POLIOMYELITIS AS COMPARED WITH THE SYMPTOMS OF DIAGNOSTIC HOSPITALIZED CASES OF THE DISEASE BEFORE PARALYSIS DEVELOPED OR IN CASES WHICH DEVELOPED NO TRUE PARALYSIS

SYMPTOMS	CONTACT ILLNESSES (%)	KNOWN CASES OF POLIOMYELITIS	
		PRECEDING PARALYSIS (%)	WITHOUT PARALYSIS (%)
Fever	49	80	82
Nausea and vomiting	36	49	58
Sore throat	29	21	24
"Cold"	21	10	11
Headache	16	55	63
Diarrhea	11	5	5
Cough	2	0	4
Drowsiness	1	10	14
Dizziness	1	4	11
Other	3	1	1
Symptoms referable to central nervous system			
Stiff neck and back	8	86	100
Extremities	13	37	50
Bulbar symptoms	0	5	10

#### AGE DISTRIBUTION

Among the total group of illnesses associated with the cases of poliomyelitis, there was a wide variation in the age of the individuals. No age group was conspicuous by its absence, but instead there were individuals ranging in age from a few weeks to over 70 years, whose illnesses were so closely linked to known cases of the disease as to indicate that in all probability they, too, were caused by the virus of poliomyelitis. When the age distribution curve of the 1,123 associated illnesses was plotted against that of the 1,074 reported cases of the disease, a close similarity was found. This is shown in Fig. 1, the data being presented in Table V. The age of highest incidence for both was from 5 to 9 years. The only significant difference noted was a slight increase in the proportion of associated illnesses in the 25- to 39-year age groups. This was found to be caused by the large number of parents of the younger and most susceptible age group, and probably indicates an unusually high degree of exposure among parents. The distribution of the various age groups in the general population is also shown for comparison. The similarity of the age-distribution curves of the two groups of illnesses, both of which occurred during the summer season, is interesting as confirmatory evidence of the poliomyelitic nature of the associated minor illnesses.

Since individuals of all ages are included in the group of contact illnesses, although paralytic poliomyelitis is particularly common in children, the ques-

tion arises as to whether age per se is related to the symptomatology resulting from infection with the virus. To answer this question, an age-distribution table of the individuals showing each symptom has been set up. The data are presented in Table VI. It will be seen that in the youngest age group,

TABLE V. AGE DISTRIBUTION OF POPULATION, POLIOMYELITIS CASES, AND MINOR ILLNESSES IN BUFFALO CITY AND ERIE COUNTY

AGE	POPULATION		REPORTED POLIOMYELITIS		MINOR ILLNESSES	
	THOUSANDS	PER CENT	NO. OF CASES	PER CENT	NUMBER	PER CENT
0-4	54.3	6.8	249	23.2	226	20.1
5-9	57.4	7.2	297	27.6	312	27.8
10-14	66.8	8.4	259	24.1	190	16.9
15-19	70.7	8.9	125	11.6	61	5.5
20-24	70.0	8.8	49	4.6	22	2.0
25-29	67.3	8.4	43	4.0	53	4.7
30-34	62.7	7.9	31	2.9	66	5.9
35-39	60.1	7.5	15	1.4	56	5.0
40-44	60.4	7.5	1	0.1	28	2.5
45-49	58.5	7.3	3	0.3	8	0.7
50-54	50.2	6.3	1	0.1	5	0.4
55-59	37.7	4.7	1	0.1	5	0.4
60-64	29.2	3.7			5	0.4
65-69	21.8	2.7			4	0.4
70-74	15.3	2.0			1	0.1
75-over	15.2	1.9				
Unknown					81	7.2
Totals	798.3	100	1,074	100	1,123	100

TABLE VI. AGE DISTRIBUTION OF THE INDIVIDUAL SYMPTOMS OF 1,123 CLOSE ASSOCIATES OF PATIENTS WITH POLIOMYELITIS\*

AGE	FEVER (%)	NAUSEA VOMITING (%)	SORE THROAT (%)	HEADACHE (%)	"COLD" (%)	DIARRHEA (%)	SYMPTOMS SUSPICIOUS OF POLIO (%)	POLIO (%)
0-9	61.0	50.8	44.0	25.4	41.2	45.6	29.8	50.8
10-19	21.0	22.0	27.4	32.8	18.0	15.4	26.0	35.6
20-29	3.2	6.0	6.4	9.6	7.6	7.8	9.2	8.6
30-39	5.2	8.8	9.0	19.4	16.2	14.6	16.0	4.4
40-49	1.4	1.4	1.0	2.4	4.6	7.0	6.6	0.4
50-59	0.6	1.0	0.4	1.2	1.8	1.8	1.6	0.2
60-69	0.0	0.8	0.6	0.0	0.0	2.6	0.0	0.0
Unknown	7.6	9.2	11.2	9.2	10.6	5.2	10.8	0.0
Totals	100	100	100	100	100	100	100	100

\*The boxed-in figures are those which are highest for the age group.

fever occurred in a particularly high percentage as compared with the other symptoms. Headache, on the other hand, was noticeably less common. These peculiarities of the younger age group are in no way indicative of a poliomyelitic infection, but are characteristic of the childhood type of reaction to any infection. It is interesting to note that headache and symptoms suggestive of the clinical disease were more common in the 10- to 39-year age groups, while diarrhea was somewhat more prevalent in the older age groups. The table also suggests that the clinical disease affected the 10- to 19-year-old group in the present epidemic out of proportion to other individual symptoms. This,

however, may possibly be a characteristic of the local epidemic. The results suggest that in attempts to detect the mildest forms of poliomyelitis, nausea, vomiting, and sore throat will be encountered at all ages in about the same proportion. However, fever is more characteristic of young children, diarrhea of the older age groups, while headache and symptoms suggestive of involvement of meninges and extremities are more common in the middle group or in young adults.

In view of the similarity of symptoms of the minor illnesses among the contacts to the early phase of the clinical disease, the problem of recognition of the one becomes essentially the same as early diagnosis of the other. Although it is to be hoped that methods for laboratory confirmation of the diagnosis will someday become available to all physicians, at present clinical observation and judgment remain as the only readily available means for diagnosing infections with the virus of poliomyelitis, mild, abortive, and severe, and, consequently, for planning a program for the control of epidemics. The present report has attempted to supply the practicing physician with a few additional aids in meeting his difficult diagnostic problems.

#### DISCUSSION

The cyclical epidemics of poliomyelitis are judged at the present time by the number of cases reported to departments of health. Yet a comparison of the proportions of paralytic and nonparalytic cases reported in different localities reveals a wide variation in the attitudes of physicians as to what constitutes a reportable case of the disease. In some localities, 99 per cent of the cases have evident paralysis; in others, only 17 per cent.<sup>5</sup> In some communities, cases which do not exhibit outspoken signs are ignored in order to allay public alarm; in others, physicians are on the lookout for early and mild symptoms regardless of the later course of the disease. Such differences in opinion are of more than academic interest, for they indicate the inadequacy of our present criteria for diagnosis and, because of this, allow no foundation on which to judge public health measures. It becomes essential, therefore, to obtain a clear picture of all the symptoms which may arise from an infection with the virus of poliomyelitis and not to confine attention to those cases presenting paralysis or even to patients showing changes in the spinal fluid.

From the data presented here and from numerous reports in the literature<sup>2</sup> there has come a body of evidence which leaves no room for doubt concerning the existence of mild cases of "abortive" poliomyelitis which are impossible to distinguish clinically from infections due to common bacterial pathogens. Usually they pass as unexplained fevers, attacks of nausea and vomiting, respiratory infections, or "grippe." Yet from such individuals the virus may be acquired by a sibling or friend who develops the paralytic form of the disease. The problem of preventing the spread of poliomyelitis, therefore, resolves itself in part into a widespread awareness of the mild forms which the disease may assume. Since there are no simple laboratory aids for confirming the diagnosis on a large scale as is possible with typhoid fever and



diphtheria, progress must be based on careful clinical observations at the present time.

How, then, is the clinical diagnosis of poliomyelitis to be made? Other central nervous system inflammations and, in particular, the various types of encephalitis may, of course, simulate the picture, and in the absence of an epidemic be difficult to differentiate. However, in individuals presenting meningeal and paralytic symptoms and showing the characteristic changes in the spinal fluid the diagnosis is immediately clear. Even in the absence of weakness or paralysis, signs of meningeal irritation with a spinal fluid showing a moderate increase in cells and protein may usually be considered diagnostic, especially in the presence of other cases in the community or following exposure to an epidemic area. Brainerd and associates<sup>6</sup> have pointed out that many cases show persistent spasm of certain groups of muscles with or without other symptoms, and that this is found in almost no other condition. A careful examination may detect mild grades of spasm, weakness, or incoordination which would be missed in a more cursory inspection. Especially in the presence of an epidemic, one may with fair confidence diagnose poliomyelitis whenever persistent muscle spasm, weakness, incoordination *or* change in the spinal fluid is noted in conjunction with an acute illness. It should be noted that numerous clinicians<sup>7</sup> have reported severe and even fatal poliomyelitis without changes in the spinal fluid.

The greatest problem naturally arises in diagnosing poliomyelitis in individuals who show only an acute illness without any of the signs pointing to the specific virus or central nervous system infection. In the absence of laboratory aids, help can be obtained from information of several types. (a) Experiences such as those presented in the body of this report suggest that the following symptoms either alone or in various combinations may result from infection with the virus of poliomyelitis: fever, nausea and vomiting, sore throat, nose cold, mild diarrhea, and headache. Whether still milder symptoms may also occur is not clear, but from epidemiological observations on nearly 1,000 families in which poliomyelitis has developed, we have gained the distinct impression that individuals with such "milder" symptoms or so-called healthy carriers are rarely, if ever, responsible for transmitting the disease. Casey<sup>8</sup> has come to a similar conclusion. From the viewpoint of public health, therefore, the main problem appears to center around the symptoms of an acute illness. (b) When the symptoms, mentioned in (a), result from agents other than the virus of poliomyelitis, the incubation period is shorter—almost always from one to three days. In contrast, the period between exposure and symptoms in poliomyelitis is usually from one to two weeks, and occasionally longer. A history of contact with an illness having a latent interval of from one to three weeks reinforces the suspicion that the illness in question may be mild poliomyelitis. (c) Since it has been estimated by various workers<sup>9</sup> that during an epidemic period there are from six to twenty illnesses of a mild nature caused by the virus for every individual diagnosed as having the disease, the presence of paralytic cases in a family or community should

attract attention to the minor sicknesses and arouse suspicions concerning the etiologic nature. (d) Finally, poliomyelitic infections are relatively more common in warm weather than in cold, a fact which is opposite from the seasonal periodicity of other common infections. While it is impossible to establish the diagnosis in mild illnesses without laboratory confirmation, these four guides offer a helpful basis for judgment.

If physicians are to make the diagnosis of poliomyelitis on all individuals whose symptoms give rise to suspicions as already discussed, an entirely new problem presents itself to our public health agencies whose function it is to prevent or control epidemics of all kinds. Should physicians be urged to report poliomyelitis whenever suspicions are aroused, even though no means exist for confirmation? Or should minor illnesses of uncertain nature be ignored? Three alternatives are open. The first, which is now in vogue in most states, is to tabulate the statistics of an epidemic for general purposes only, but to carry out no definite program of control. This stand has been based on the futility of experiences which have attempted to check the spread of the disease by quarantine of the reported cases. In the light of present-day knowledge such quarantine could have little, if any, value. The second alternative would be to insist on the reporting and isolation of all suspicious illnesses. Since the disease appears to be spread largely through contact with individuals who have active symptoms, theoretically, at least, rigid quarantine should be effective. In practice such a policy has proved impossible to carry out, both because of the disinclination of physicians to report the diagnosis on insecure evidence and the futility of measures in such attempted drastic and widespread quarantine. A third alternative would be to encourage physicians to report even the mildly suspicious illnesses but to depend on public education for control. Certain facts concerning the methods of spread are known, which could be brought to the attention of families, neighborhoods, and communities during an epidemic, and should enable them to carry out any local measures which, in conjunction with local health officials, would be deemed advisable. This last procedure would appear to be more practical and probably more effective also than either of the foregoing. It would place the responsibility and initiative with small local groups rather than with the unsatisfactory police power of a health department.

#### SUMMARY AND CONCLUSIONS

Illnesses of 1,123 close contacts of patients with poliomyelitis have been studied.

The most common symptoms of the group were fever, nausea and vomiting, sore throat, and a "cold." Headache, symptoms referable to the central nervous system, and diarrhea were encountered less frequently. Combinations of one or more were usually found.

The similarity of these symptoms to those occurring in the preparalytic state or in the nonparalytic form of clinical poliomyelitis was pointed out.

All ages were affected, the oldest being 74 years, the youngest 6 weeks. The age distribution was similar to that of the reported cases of poliomyelitis occurring during the same season.

When the various symptoms were reviewed in respect to the age of the individuals concerned, it was noted that fever was particularly common in children below the age of 10 years, headache among the 10- to 40-year group, and diarrhea in the older individuals. Nausea, vomiting, and sore throat affected the various age groups in approximately the same proportion.

Although no laboratory aids are readily available to verify clinical diagnoses of poliomyelitis infections, the following circumstances assist in reaching a conclusion: (a) a similarity of the symptoms to those known to occur in mild illnesses caused by the virus; (b) evidence of an incubation period of from one to three weeks; (c) the presence of known cases of poliomyelitis in the neighborhood; (d) occurrence during the season of warm weather.

It is suggested that if the mild as well as the severe cases of infection with the poliomyelitis virus were reported to departments of health, a more adequate program for public education and control of the disease could be evolved.

#### REFERENCES

1. Wickman, O. I.: Acute Poliomyelitis, Nerv. & Ment. Dis. Monograph, Serial 16, New York, 1913.
2. a. Paul, J. R., Salinger, R., and Trask, J. D.: "Abortive" Poliomyelitis, J. A. M. A. 98: 2262, 1932.  
 b. Trask, J. D., Vignec, A. J., and Paul, J. R.: Poliomyelitis Virus in Human Stools, J. A. M. A. 111: 6, 1938.
- c. Paul, J. R., and Trask, J. D.: The Virus of Poliomyelitis in Stools and Sewage, J. A. M. A. 116: 493, 1941.
- d. Piszczek, E. A., Shaughnessy, H. J., Zichis, J., and Levinson, S. O.: Acute Anterior Poliomyelitis; Study of Outbreak in West Suburban Cook County, Ill.; Preliminary Report, J. A. M. A. 117: 1962, 1941.
- e. McClure, J. Y., and Langmuir, A. D.: Search for Carriers in Outbreak of Acute Anterior Poliomyelitis in Rural Community; Incidence of Virus in Feces, Am. J. Hyg. 35: 285, 1942.
- f. Pearson, H. E., Brown, G. C., Rendtorff, R. C., Ridenour, G. M., and Francis, T., Jr.: Studies of the Distribution of Poliomyelitis Virus. III. In an Urban Area During an Epidemic, Am. J. Hyg. 41: 188, 1945.
3. Smith, M. L., Bridge, E. M., Underwood, H. E., and Dale, G. E.: A Study of the Origin of an Epidemic of Poliomyelitis, J. A. M. A. 129: 1150, 1945.
4. Wilson, May G.: Society Report, N. Y. Academy of Medicine, Section on Pediatrics, Arch. Pediat. 33: 850, 1933.
5. Dauer, C. C.: Incidence of Poliomyelitis in the United States in 1944, Pub. Health Rep. 60: 633, 1945.
6. Brainerd, H., Katz, H. J., Rowe, A. P., and Geiger, J. C.: The Clinical Manifestations of Poliomyelitis, J. A. M. A. 128: 718, 1945.
7. a. Trask, J. D., and Harper, P. K.: A Diagnostic Problem in Poliomyelitis; A Consideration of Typical and Suggestive Cases Showing Normal Spinal Fluid, Yale J. Biol. & Med. 5: 155, 1932.  
 b. Wilson, J. L.: Poliomyelitis, The Oxford Medicine, Oxford University Press, New York 5: 107, 1940.
8. Casey, A. E.: Observations on an Epidemic of Poliomyelitis, Science 95: 359, 1942.
9. a. Paul, J. R., Salinger, R., and Trask, J. D.: Studies on the Epidemiology of Poliomyelitis. II. The Incidence of Abortive Types of Poliomyelitis, Am. J. Hyg. 17: 601, 1933.  
 b. McClure, G. Y., and Langmuir, A. D.  
 c. Smith, M. L., Bridge, E. M., and associates.

## THE EFFECTS OF ACTIVE IMMUNIZATION OF THE MOTHER UPON THE OFFSPRING

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THE human placenta is of the hemochorionic type characterized by the intimate relation of the fetal capillaries and the maternal circulation.<sup>1</sup> The trophoblast is the parenchyma and unit of the placenta, constituting the essential tissue which sustains the growth and nutrition of the embryo by securing nutriment from the maternal organism.<sup>2</sup> The endothelium of the bulging fetal capillaries is closely applied to a thinned-out sheet of syncytial trophoblast, a structural mechanism admirably adapted for active and direct exchange of gases and metabolites between the intervillous space and the fetal circulation. This relationship bears comparison with the cytological features of the pulmonary alveoli and the kidney glomeruli.<sup>3</sup> The trophoblast, clothing the chorionic villi, is also the barrier between mother and fetus, for the syncytium has selective and phagocytic properties which regulate the exchange between mother and fetus, and fetus and mother.

To all intents and purposes, the hemochorionic placenta is composed of myriads of semipermeable membranes, obeying the physicochemical laws of such membranes. The size of the molecule largely determines what traverses and what fails to pass the placental barrier, which, as has been noted, has the capacity of halting the passage of foreign material.<sup>4</sup> So we observe the free passage and equal distribution of chemical substances and soluble drugs between maternal and fetal circulations.<sup>4, 5</sup> The same principles and findings hold true for antibodies, for it has long been recognized that antitoxins, such as diphtheria, tetanus, and scarlet fever, are approximately equal in the blood of mothers and newborn babies.<sup>6</sup> Similarly, isohemolysins, isoagglutinins,<sup>4, 5, 8</sup> and other agglutinins<sup>9</sup> and hormones<sup>5</sup> may readily traverse the placenta. The antibodies against poliomyelitis,<sup>10</sup> influenza, lymphogranuloma venereum,<sup>12</sup> and other virus diseases<sup>5, 12</sup> have been transmitted from mother to fetus. Antistreptolysin,<sup>14</sup> staphylococcus antitoxin,<sup>15</sup> and antipneumococcal antibodies<sup>16</sup> also readily gain entrance into the fetal circulation if the mother possesses such antibodies. The present concept of the pathogenesis of erythroblastosis fetalis is based upon the transmission of isohemolysins from mother to fetus.<sup>8</sup>

It is worthy of emphasis that the uninjured chorion is relatively impervious to colloidal and particulate matter. Maternal antibodies, however, if present, readily pass the placental filter, but toxins meet resistance, and foreign proteins are normally phagocytosed by chorionic cells, the protective barrier of the fetus against bacteria and viruses.<sup>5, 13</sup> Failure of this action may, on occasions, lead

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to the death of the fetus, to intrauterine disease or malformations manifesting themselves in the baby at birth or some time thereafter, or to processes of sensitization with various allergic expressions.<sup>13, 17</sup>

This evidence logically leads to the conclusion that the immune properties of the newborn depend upon the immunologic status of the mother. It is as rational to remedy maternal immunologic deficiencies as to correct maternal lack of protein, minerals, vitamins, anemia, or any other deficiency which may be deleterious to the welfare of the unborn baby. Appropriate studies should be undertaken during pregnancy to reveal remediable deficiencies, including immunologic ones, which are pertinent to the resistance of the offspring.

TABLE I. RESULTS OF SCHICK TESTS AT DIFFERENT AGES (1914-1923)\*

AGE	PER CENT SCHICK POSITIVE	PER CENT SCHICK NEGATIVE
Newborn	16	84
0- 3 months	28	72
3- 5 months	43	57
6- 7 months	57	43
7- 8 months	63	37
8- 9 months	84	16
9-10 months	93	7
10-11 months	87	13
11-12 months	91	9
1- 3 years	83	17
4- 6 years	61	39
6- 7 years	50	50
7- 8 years	44	56
8- 9 years	37	63
9-10 years	32	68
10-11 years	29	71
11-12 years	28	72
12-13 years	24	76
13-14 years	23	77
14-15 years	20	80
15-16 years	18	82
16-17 years	18	82
Over 17 years	14	86

\*B. Schick in *Brenneman's Practice of Pediatrics*.

Diphtheria and pertussis are the two most important preventable contagious diseases of infancy. There has been a subtle change in diphtheria susceptibility in the past generation, a change not properly evaluated. Whereas twenty to thirty years ago 80 to 90 per cent of adults were proved immune to diphtheria,<sup>18</sup> in recent years only about 50 per cent of adults have been shown to be immune.<sup>19, 20</sup> By means of Schick tests and titration of circulating antitoxin, abundant testimony has been collected by different investigators in diverse localities to establish the changed immunologic status of the adult population to diphtheria.<sup>19, 20, 21, 22</sup>

Analysis of the data, compiled by Schick largely from statistics in Vienna and from New York, revealed that in the period from 1914 to 1923, 86 per cent of adults were immune to diphtheria, as were the newborn babies of that generation. The era of prophylactic immunization then began with interesting and significant changes. It gradually came to light that the passage of years produced a waning of artificially induced immunity (Table II). After three

TABLE II. DURATION OF DIPHTHERIA IMMUNITY\*

INTERVAL AFTER IMMUNITY	SCHICK POSITIVE (%)	SCHICK NEGATIVE (%)
6 mo	0.4	99.6
1 yr.	3	97
3 yr.	8	92
5 yr.	34	66

\*From Brandon and Fraser, Studies of ninety-four children Schick negative after three toxoid injections at three-week intervals.

years, when only 8 per cent of successfully immunized children became Schick positive, the percentage increased precipitously so that at the end of five years, between 25 and 35 per cent of the immunized groups became Schick positive.<sup>20, 24</sup> This finding has given rise to the approved practice of a booster reinjection of diphtheria toxoid (and other antigens) at intervals of three years. Since this practice is far from universal after 6 years of age, the adult has suffered further loss of immunity (Table III). Schick tests, confirmed on occasion by blood antitoxin titrations, have demonstrated that from 30 to 87 per cent of adults in different regions are susceptible to diphtheria. Investigations in our clinic on young, pregnant women, nearly all of whom had been immunized in early childhood and were Schick negative on entering school, substantiate the recent statistics that about 50 per cent of adults are no longer immune to diphtheria. Obviously this increased susceptibility must necessarily be reflected in corresponding lack of immunity in the newborn babies, since such immunity is passively transferred. Recent data and our own studies of diphtheria immunity in mother and offspring support this contention.<sup>20, 21</sup> (Table IV.)

TABLE III. DURATION OF SCHICK IMMUNITY

DATE	AUTHOR	NO TESTED	IMMUNITY STATUS	SCHICK POSITIVE (%)
1936	Fraser and Brandon <sup>24a</sup>	94	5 yr.	34
1938	Schwartz and Janney <sup>24b</sup>	145	6 yr.	22
1941	Lewis, J. T. <sup>22</sup>	51	51 to 53 mo	37
1943	Duke and Stott <sup>24c</sup>	164	5 yr.	25

TABLE IV. DIPHTHERIA IMMUNITY IN ADULTS (1932-1944)

AUTHORS	DATE	REGION	NUMBER	AGE GROUP	SCHICK POSITIVE (%)
Cooke and Sharma <sup>25a</sup>	1932	St Louis	643	30 years	30
Liebling and associates <sup>21</sup>	1941	Chicago	—	25 years	52.8
Campbell <sup>25b</sup>	1941	Halifax	405	20 years	59
	1941	Halifax	243	18 years	80
	1941	Halifax	250	25 years	55
	1941	Halifax	—	22 years	71
	1941	Halifax	558	Adult	87
Wishart <sup>25c</sup>	1943	Canada	74	20 years	52.7
Karelitz and Moloshok <sup>25b</sup>	1944	Americans in Africa	1,293	20-25 years	28.6
Wright and Clark <sup>25a</sup>	1944	London	250	28 years	51.6
	1944	London	62	31 years	58
Bull U. S. Army <sup>25b</sup>	1944	U S	2,933	20-30 years	44
Colien and associates	1946	New York City	175	Pregnant women	52

The reason for the waning immunity of the adult against diphtheria has been ascribed to the present lack of contact with the diphtheria bacillus, a sequel of prophylactic immunization, and the decline of diphtheria. So infrequently do adults today come in contact with the toxogenic bacilli that the circulating antitoxin often falls below the critical titer for a negative Schick test.<sup>22, 25</sup> The persistence of artificial immunity depends upon periodic artificial restimulation or continuation of the immune response by exposure to the diphtheria environment. Epidemiologists, aware of recently increasing diphtheria outbreaks, have come to the conclusion that the diphtheria problem of the future is concerned with older children and adults, for they have borne the brunt of recent diphtheria epidemics.<sup>23, 25</sup>

TABLE V. STAPHYLOCOCCUS ANTITOXIN CONTENT—UNITS PER CUBIC CENTIMETER\*

MATERNAL	FETAL	INFANTILE	AGE OF INFANT
122	248	72	4 weeks
70	86	94	4 weeks
58	57	10	4 weeks
51	77	23	4 weeks
48	190	38	4 weeks
91	93	29	8 weeks
-	80	20	8 weeks
11	22	3	8 weeks
23	41	7	8 weeks
93	100	10	8 weeks

\*Bryce and Burnet.<sup>15a</sup> Illustrates passage of staphylococcus antibodies from mother to baby; decrease in the older infants.

While the Schick test is not an exact measurement of antitoxin content, it has an exceptionally good correlation with immunity against diphtheria.<sup>22</sup> Since the skin of a newborn baby is not fully reactive, immunity in the baby can be better evaluated by performing Schick tests on the mother.<sup>20, 21</sup> This practice is not only accurate but obviates the time-consuming antitoxin titrations which yield no practical advantage over the Schick tests.<sup>20, 21, 22</sup> If a pregnant mother is Schick positive, she should be injected with diphtheria toxoid to increase her immunity to a level (the Schick negative state) which is certain to confer adequate immunity upon the baby.

Active immunization of the pregnant woman against diphtheria has already been performed with gratifying results. Mothers formerly Schick positive, with low blood diphtheria antitoxin content, were converted by active immunization during the latter part of pregnancy to immunity against diphtheria.<sup>21</sup> It should be remembered that the Schick test itself, by virtue of the injected toxin, is not only a measure of antitoxin content, but may be a stimulating antigen, and an effective boosting agent in those who have previously been inoculated with toxoid or stimulated by exposure to carriers.

Just as the easily performed Schick test and the precision of antitoxin determinations have yielded abundant data about diphtheria immunity, so has the absence of such tests accounted for the paucity of authentic data about pertussis immunity in the adult and the infant. It was only five years ago that relatively accurate data was collected, which pointed to the fact that only 15 to 30 per cent of adults have protective antibodies against pertussis.<sup>26</sup> Similar

studies of a small series of newborn infants suggested that about 15 per cent have some degree of immunity against whooping cough.<sup>23</sup> This low percentage of infantile protection receives clinical confirmation from the frequent incidence of pertussis in the infant,<sup>25</sup> when it is attended by the highest mortality. A ten-year survey of whooping cough at Willard Parker Hospital revealed that 5 to 6 per cent of its incidence occurs in the first six months of life.

Lack of immunity in the mother results in susceptibility to pertussis of the infant. It occurred to one of us (P. C.) that it was not only desirable but feasible to protect the infant against pertussis by inoculating the mother during pregnancy with a potent pertussis vaccine. It had been amply demonstrated that immunity can be produced by such vaccination.<sup>26</sup> Because of the evidence detailed at the outset, we believed that antibodies so produced would be transmitted through the placenta to the baby. Accordingly, 170 women were injected at two-week intervals from the sixth to the eighth month of pregnancy in doses totaling from 90 to 150 billion of pertussis vaccine. Immunologic studies of thirty women of this group demonstrated that all developed high titers of immune bodies following such vaccination, and that these antibodies were regularly transmitted to their babies in a titer quantitatively of the same order. Similar studies repeated at intervals of five and one-half to ten months in a group of ten mothers and babies (Table VI) showed that active immunization of the

TABLE VI. RETESTS OF VACCINATED MOTHERS AND THEIR BABIES\*

SERIAL	NAME	BLED	PERIOD	RESULT			
				AGGLU TINATION	C. F.	MOLSE PROTECT SURV.	PER CENT
C2	Mrs. D. B.	3/18/42	9 mo. after vaccination	800	0.02	2/8	25
	Baby D. B.	3/18/42	8½ mo. old	0	0	N.T.†	
C3	Mrs. P. B.	2/26/42	8 mo. after vaccination	10	0.02	0/10	0
	Baby P. B.	2/26/42	6½ mo. old	0	0	0/10	0
C5	Mrs. M. E.	4/28/42	10 mo. after vaccination	75	N.T.	8/10	80
	Baby M. E.	4/28/42	8½ mo. old	0	N.T.	0/4	0
C6	Mrs. G.	2/19/42	8½ mo. after vaccination	??	N.T.	N.T.	
	Baby G.	2/19/42	7 mo. old	?		N.T.	
C12	Mrs. A. M.	3/18/42	8½ mo. after vaccination	600	0	5/10	50
	1st Twin P. M.	3/18/42	8½ mo. old	slide	0	1/6	0
	2nd Twin S. M.	3/18/42	8½ mo. old	slide - 0	0	N.T.	
C15	Mrs. T.	2/26/42	8½ mo. after vaccination	150	0.02	6/10	60
	Baby T.	2/26/42	8 mo. old	0	0.02	0/10	0
C20	Mrs. S. K.	4/28/42	9½ mo. after vaccination	25	N.T.	6/10	60
	Baby H. K.	4/28/42	8½ mo. old	0	N.T.	0/10	0
C25	Mrs. E. A.	4/12/42	9 mo. after vaccination	400	N.T.	9/10	90
	Baby E. A.	4/12/42	8 mo. old	0	N.T.	0/9	0
C36	Mrs. H. L.	3/12/42	7½ mo. after vaccination	0	0.02‡	3/10	30
C39	Mrs. M. V.	3/12/42	8 mo. after vaccination	600	0.02	4/10	40
	Baby M. V.	3/12/42	5½ mo. old	0	0	N.T.	

\*Illustrates retention of antibodies in mothers actively immunized and loss by babies passively immunized.

†Not tested.

‡Strongly hemolyzed.



mother resulted in the persistence of antibodies, while it may be assumed that the babies retained little or none of their antibodies, passively obtained. Larger doses of the vaccine may yield a more lasting immunity for the baby, a hypothesis we shall test.

The follow-up studies regarding the incidence of pertussis in 100 babies of immunized mothers were compared with an equal number of babies of unimmunized mothers. In the latter group, in the first six months of infancy, there were six exposures resulting in three cases of whooping cough. During the same age period of the immunized group there were eight exposures, three due to close contact, but no cases of whooping cough developed. In the second six months of life each group yielded two cases of whooping cough. Since our studies had revealed that the immunity of the babies unlike the mothers, does not persist after 5 to 6 months of age, the occurrence of pertussis in our immunized group in the second six months of life occasioned no surprise. While our data and numbers are too meager and too incomplete to lead to conclusions, the results of the incidence of whooping cough, within limits, are in keeping with the expectancy of passive immunization.

Three groups of investigators using different immunologic techniques have obtained results which led to the conclusion that pertussis antibodies are transmitted by the placental route to the newborn baby.<sup>31</sup> One group, employing the opsonocytophagic method, presented evidence that pertussis vaccination during pregnancy increases the opsonophagocytic powers of the mothers which were quantitatively transmitted to their babies. No further studies of the persistence of the increased opsonophagocytosis, nor a clinical follow-up of the babies prenatally immunized, were reported.

The timing of the injections is of the utmost importance. We administered our vaccine during the last third of pregnancy, because during that period both placental and fetal circulations are amply developed for the proper circulation and filtration of the diffusible antibodies.<sup>2, 4, 32</sup> We aimed to complete our prophylaxis six weeks before term, for both pertussis and diphtheria immunization yields its peak of immune titers four to eight weeks after the termination of adequate prophylaxis.<sup>21, 33</sup> By such timing, we planned to have the mother reach the pinnacle of immunization at term so that the baby could be endowed at birth with the highest antibody content. Our data support the success of our timing and termination of our prophylaxis.

Passive immunity of the baby induced by active immunization of the mother is the best available method for producing immunity in the young infant. Studies, just after birth, of the electrophoretic pattern of the serum proteins of mothers and their babies lend support to this opinion.<sup>34</sup> Immunity has been demonstrated to reside in the gamma globulin fraction, and it is precisely in this and only in this antibody fraction that the baby equals or even surpasses its mother's component. This finding is consistent with the maternally conferred immunity of the newborn. It is well known among immunologists that the newborn and very young infant is a poor antibody producer.<sup>35</sup> Attempts at active immunization during this early age period have yielded little or no demonstrable results.<sup>36</sup>

When multiple antigens are simultaneously injected, the antibodies called into production are quantitatively in ratio to the potency of the antigens.<sup>37</sup> Diphtheria toxoid is a very potent antigen, as is the pertussis vaccine (to a lesser degree), but the Rh factor is a relatively weak antigen. It is sound theory and a hopeful practice to administer combined diphtheria pertussis vaccine early in pregnancy, for by so doing, the production of anti-Rh antibodies may be suppressed. This method of counterimmunization has already been attempted in women with a history or background of Rh sensitization, but data are insufficient to lead to definite conclusion.<sup>37</sup> This procedure, nevertheless, is an added attraction and argument for active immunization during pregnancy for the benefit of the offspring, but it is important to note that the inoculations begin during the first trimester instead of the last trimester of pregnancy.

From our observations we can definitely state that active maternal immunization has no observable deleterious effects upon the offspring. The mother, however, may often suffer local discomfort for a brief period, and at times fever and systemic reactions develop, but these reactions have no ill effects upon the pregnancy. An intradermal test with a one to ten dilution of diphtheria toxoid is first performed on all Schick positive cases (Moloney test). If this reaction is definitely positive within one-half hour, either diphtheria toxoid is omitted if the reaction is very marked, and plain pertussis vaccine given, or the initial dose of 0.1 c.c. diphtheria toxoid is followed by 0.25 c.c., 0.5 c.c., and 1 c.c. added to the pertussis vaccine in the same syringe. We favor the use of a fluid diphtheria toxoid combined with a pertussis vaccine containing 15 billion bacilli per c.c. beginning with 1 c.c., followed with 2 c.c. for two doses twice, and then 3 c.c., totaling 120 billion pertussis bacilli. In sensitive cases the diphtheria toxoid in increased dosage is added to pertussis vaccine as described. This method causes fewer and less reactions than the alum preparations which, in addition to producing greater reactions, often leave annoying and embarrassing nodules of which the women complain, and because of which they may object to the continuation of immunization.

Our present program is to take inventory of the immunologic status of the pregnant woman at the earliest opportunity. Deficiencies in immunity against diphtheria, pertussis, or any remediable infection which may be endemic such as influenza, streptococcus infections, may then be corrected by appropriate combined immunization of the mother in the latter part of pregnancy. The maternal immunity so induced, as has been frequently demonstrated, will be transmitted to the infant to endure for the first few months of life. At the age of 6 months, appropriate active immunization should be administered to the infant. Our scheme of active combined maternal immunization is not unlike the prophylactic, combined immunizations which the Armed Services rendered its members during World War II with such effective and gratifying results.<sup>38</sup>

#### SUMMARY AND CONCLUSIONS

1. The human placenta readily transmits diffusible substances such as anti-toxins and antibodies.

2. Lack of immunity in the mother is reflected in a corresponding lack of immunity of her baby.

3. Apparently as a result of childhood prophylaxis, women today lack immunity to diphtheria in about 50 per cent of cases in contrast to 85 per cent immunity in the preimmunization era of the past generation.

4. About 80 per cent of women and about 85 per cent of babies are not immune to whooping cough as demonstrated by lack of protective antibodies.

5. Since the young infant does not produce a proper titer of antibodies by active immunization, it should be protected during the perilous first few months of life by passive immunization.

6. Active immunization of the mother in the last of trimester of pregnancy will confer passive immunity upon the offspring for the first few months of his life against diphtheria, whooping cough, and probably against other diseases for which we have effective vaccines.

7. Vaccine and toxoid therapy during pregnancy may serve to suppress formation of anti-Rh antibodies. This method of counterimmunization is an additional argument for active immunization in pregnancy, but for this purpose the inoculations should be given from the first trimester of pregnancy through the last.

8. Local reactions occur frequently, but systemic effects are infrequent.

9. The procedure of active immunization during pregnancy is harmless, for we have observed no ill effects upon the babies or upon the mothers during the course of pregnancy.

10. A program is presented of combined, active, maternal immunization remedying immunologic deficiencies of the mother to the immunologic advantage of the offspring.

#### REFERENCES

1. Windle, F.: *Physiology of the Fetus*, Philadelphia, 1940, W. B. Saunders Company.
2. Wislocki, G. B., and Bennett, H. S.: *Histology and Cytology of the Human and Monkey Placenta, with Special Reference to Trophoblast*, *Am. J. Anat.* 73: 335, 1943.
3. Wislocki, G. B.: Some Observations on the Cytology of the Trophoblast, *Proc. Conf. Probl. Human Fertil.*, p. 134, 1943.
4. a. Needham, J.: *Chemical Embryology*, London, 1931, Cambridge University Press, vol. 3.  
b. Wiener, A. S., and Silverman, I. J.: Permeability of the Human Placenta to Antibodies, *J. Exper. Med.* 71: 21, 1940.
5. a. Pommerenke, W. T.: Placental Interchange: On the Concentration of Certain Nitrogenous Substances in the Blood, Before and After Passing Through the Placenta, *J. Clin. Investigation* 15: 485, 1936.  
b. Thompson, H. E., Jr., and Pommerenke, W. T.: Placental Interchange: Comparison of Total Base Concentration of the Fetal and Maternal Blood at Parturition, *J. Clin. Investigation* 17: 609, 1938.
- c. Pohl, H. A., Flexner, L. B., and Gellhorn, A.: The Transfer of Radioactive Sodium Across the Placenta of the Goat, *Am. J. Physiol.* 134: 388, 1941.
- d. Speert, H.: The Passage of Sulfanilamide Through the Human Placenta, *Bull. Johns Hopkins Hosp.* 63: 337, 1938.
- e. Pack, G. T., and Barker, D.: The Placental Transmission of Insulin From Fetus to Mother, *Am. J. Physiol.* 90: 466, 1922.
- f. Jones, O. P.: Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis, *Arch. Int. Med.* 68: 476, 1941.
- g. Greene, H. J., and Hobby, G.: Transmission of Penicillin Through Human Placenta, *Proc. Soc. Exper. Biol. & Med.* 57: 282, 1944.
- h. Snyder, F. F.: Placental Transmission in Relation to the Stage of Pregnancy, *Proc. Conf. Probl. Human Fertil.*, p. 144, 1943.

- G. a. McKhann, C. F., and Kapnick, I.: Immunity and Susceptibility to Disease in Early Infancy, *J. PEDIAT.* 13: 907, 1938.
- b. Ten Broeck, C., and Bauer, J. H.: The Transmission of Tetanus Antitoxin Through Placenta, *Proc. Soc. Exper. Biol. & Med.* 20: 399, 1922-1923.
7. a. Smith, C. H.: Iso-Agglutinins in the Newborn With Special Reference to Their Placental Transmission, *Am. J. Dis. Child.* 36: 54, 1928.
- b. Weiner, A. S., and Silverman, J. I.: Permeability of the Human Placenta to Antibodies, *J. Exper. Med.* 71: 21, 1941.
8. a. Levine, P., Katzin, E. M., and Burnham, L.: Isoimmunization in Pregnancy; Its Possible Bearing on Etiology of Erythroblastosis Fetalis, *J. A. M. A.* 116: 825, 1941.
- b. Levine, P.: The Pathogenesis of Erythroblastosis Fetalis, *J. PEDIAT.* 23: 656, 1943.
9. Toomey, J. A.: Agglutinins in Mother's Blood, Baby's Blood, Mother's Milk, and Placental Blood, *Am. J. Dis. Child.* 47: 21, 1934.
10. Aycock, W. L., and Kramer, S. D.: Immunity to Poliomyelitis in Mothers and Newborn as Shown by Neutralizing Tests, *J. Exper. Med.* 52: 457, 1930.
11. Rickard, E. R., and Horsfall, F. D.: Relation Between Neutral Antibodies Against Influenza a Virus in Sera of Mothers and Infants, *J. Immunol.* 42: 267, 1941.
12. Levine, S., Bullowa, J. G. M., and Scheinblum, I. E.: Antipartum Transmission of Lymphogranuloma Venereum Antibodies and Their Duration in the Infants, *J. Immunol.* 47: 439, 1943.
13. Goodpasture, E. W.: Virus Infection of the Mammalian Fetus, *Science* 95: 391, 1942.
14. a. Lichty, J. A., and Anderson, G. E.: Streptococcal Antifibrinolysins in Newborn Infants, *Am. J. Dis. Child.* 65: 60, 1943.
- b. Lippard, V. W., and Wheeler, G. W.: Placental Transmission of Antifibrinolysins and Antistreptolysins, *Am. J. Dis. Child.* 59: 61, 1936.
- c. Gordon, J. W., and Janney, J. H.: Antistreptolysin Content of the Sera in Normal Infants and Children, *J. PEDIAT.* 18: 587, 1941.
15. a. Bryce, L. M., and Burnett, F. M.: Natural Immunity to Staphylococcal Toxin, *J. Path. & Bact.* 35: 183, 1932.
- b. Murray, P. S.: Staphylococcus Toxoid, *Lancet* 1: 303, 1935.
16. Sutliff, W. D., and Finland, M.: Antipneumococcal Immunity Reactions in Individuals of Different Ages, *J. Exper. Med.* 55: 837, 1932.
17. a. Ratner, B., Jackson, H. C., and Gruell, H. L.: Transmission of Protein Hypersensitiveness From Mother to Offspring (5 papers), *J. Immunol.* 14: 249, 1927.
- b. Sherman, W. S., Sherman, W. B., Hampton, S. F., and Cooke, R. A.: Placental Transmission of Antibodies in Skin Sensitive Type of Human Allergy, *J. Exper. Med.* 72: 611, 1940.
- c. Kohn, J. L.: Measles in Newborn Infants, *J. PEDIAT.* 3: 176, 1933.
- d. Dunham, E. C.: Diagnosis of Congenital Syphilis, *Am. J. Dis. Child.* 43: 317, 1932.
- e. Shumann, H. H.: Varicella in the Newborn, *Am. J. Dis. Child.* 58: 564, 1939.
- f. John, B.: Placental Transmission of Hypersensitiveness to Ascaris Lumbricoides Actively Induced in a Pregnant Woman, *Am. J. Dis. Child.* 57: 1067, 1939.
- g. Diddle, A. W., and Stephens, R. L.: Typhoid Fever in Pregnancy, Probable Intrauterine Transmission of the Disease, *Am. J. Obst. & Gynec.* 38: 300, 1939.
- h. Neter, E. R., Siegel, D. A., and Clark, P. B.: Salmonella Choleraesuis Bacteremia During Pregnancy, *Am. J. Obst. & Gynec.* 48: 22, 1944.
- i. Swan, C., To-terin, A. L., Mayo, H., and Black, G. H. B.: Further Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, With Special Reference to Rubella, *M. J. Australia* 1: 403, 1944.
- j. Swan, C.: Study of 3 Infants Dying From Congenital Defects Following Maternal Rubella in Early Stages of Pregnancy, *J. Path. & Bact.* 56: 289, 1944.
18. a. von Groer, F., and Kassowitz, K.: Studien über die normale Diphtherie-immunität des Menschen, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 22: 405 and 23: 108, 1914.
- b. Park, W. H.: Toxin-Antitoxin Immunization Against Diphtheria, *J. A. M. A.* 79: 1584, 1922.
- c. Zingher, A.: Schick Tests Performed on More Than 150,000 Children, *Am. J. Dis. Child.* 25: 392, 1923.
- d. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 2, 1941, D. Appleton Century Company, Inc., p. 1083.
- e. Schick, B.: In Brenemann's Practice of Pediatrics, 1944, W. F. Prior Company, Inc., vol. 2, ch. 4, p. 4-6.
19. a. Cooke, J. V., and Sharma, B. M.: Schick Test in Newly Born, *Am. J. Dis. Child.* 44: 40, 1932.
- b. Campbell, P. S.: Occurrence of Diphtheria in Halifax From Oct., 1940, to Jan. 31, 1941, *Canad. J. Pub. Health* 32: 404, 1941.
20. a. Wright, G. P., and Clarke, W. M.: Schick Reactions in Recently Confined Women and Their Infants, *Brit. M. J.* 2: 146, 1944.

- b. Karelitz, S., and Moloshok, L.: Immunity to Diphtheria in Army Personnel, *War Med.* 6: 232, 1944.
- c. Wishart, F. C.: Intradermal Immunization With Diphtheria Toxoid, *Canad. J. Pub. Health* 34: 509, 1943.
- d. Cameron, G. O. W.: The Schick Test in Adults, *Canad. J. Pub. Health* 32: 414, 1941.
21. Liebling, J., Youmans, G. P., and Schmitz, H. E.: Occurrence of Diphtheria Antitoxin in the Human Pregnant Mother, Newborn Infant, and Placenta, *Am. J. Obst. & Gynec.* 41: 641, 1941.
22. a. Lewis, J. T.: *The Principles and Practice of Diphtheria Immunization*, London, 1941, Oxford University Press, ch. 3.
- b. Lewis, J. T.: Diphtheria, 1942, *J. A. M. A.* 122: 1079, 1943.
23. a. Fleming, D.: Problem of the Future, *Canad. M. A. J.* 50: 46, 1944.
- b. Mattison, B. F.: Diphtheria in an "Adequately" Immunized Community, *New York State J. Med.* 44: 2138, 1944.
- c. Fraser, D. T., and Halpern, K. C.: Antitoxic Response to Diphtheria Antigens in Children, *J. Immunol.* 33: 323, 1937.
- d. Bull. U. S. Army M. Dept. 76: 104, 1944.
24. a. Fraser, D. T., and Brandon, K. F.: Duration of Schick Immunity, *Canad. J. Pub. Health* 27: 597, 1936.
- b. Schwartz, A. B., and Janney, F. R.: The Need of Redetermining Schick Negativeness in School Children, *J. A. M. A.* 110: 1743, 1938.
- c. Lewis, J. T.<sup>21</sup>
- d. Anderson, A.: Diphtheria Immunization, Observation of Prophylactic and Duration of Immunity, *Pub. Health* 57: 131, 1944.
- e. Duke, H. L., and Stott, W. B.: Duration of Artificial Active Immunity Against Diphtheria, *Brit. M. J.* 2: 710, 1943.
25. Dudley, S. F., May, P. M., and O'Flynn, J. A.: Active Immunization Against Diphtheria, *Med. Research Council, Special Report Series No. 195*, 1934.
26. a. Mishulow, L., and associates: Pertussis Antibodies in Pregnant Women, *Am. J. Dis. Child.* 64: 608, 1942.
- b. Mishulow, L., Siegel, M., Leifer, L., and Berkey, S. R.: A Study of Pertussis Antibodies, *Am. J. Dis. Child.* 63: 875, 1942.
27. Cohen, Philip, and Scandron, J. S.: The Placental Transmission of Protective Antibodies Against Whooping Cough, *J. A. M. A.* 121: 656 (27), 1943.
28. a. Sauer, L. W.: Whooping Cough, In *Brennemann's Practice of Pediatrics*, 1941, W. F. Prior Co., Inc., vol. 2, ch. 34.
- b. Dublin, L., and Spiegelman, M.: The Control of Disease and Death in Infancy and Childhood, *Rec. Am. Inst. Actuaries*, 1941, vol. 30, part 1, no. 61.
- c. Holt, L. E., and McIntosh, R.: *Holt's Diseases of Infancy and Childhood*, ed. 2, New York, 1941, D. Appleton-Century Company, Inc., p. 1164.
29. Kohn, J. L.: Personal communication.
30. a. Singer-Brooks, C.: Pertussis Prophylaxis, *J. A. M. A.* 114: 1734, 1940.
- b. Sauer, L. W.: Whooping Cough, New Phases of Work on Immunization and Prophylaxis, *J. A. M. A.* 112: 305, 1939.
- c. Kendrick, P., and Eldering, G.: A Study in Active Immunization Against Pertussis, *Am. J. Hyg.*, sect. B 29: 133, 1939.
- d. Lapin, J. H., Cohen, P., and Weichsel, M.: Prophylactic Vaccination Against Whooping Cough, *Arch. Pediat.* 56: 590, 1939.
31. a. Rambar, A. C., Howel, K., Denenholz, E. J., Goldman, M., and Standard, R.: Studies in Immunity to Pertussis, an Evaluation of Pertussis Vaccination by Clinical Means and by the Opsonocytophagic Test, *J. A. M. A.* 117: 79, 1941.
- b. Kendrick, P., Thompson, M., and Eldering, G.: Immunity Response of Mothers and Babies to Injections of Pertussis Vaccine During Pregnancy, *Am. J. Dis. Child.* 70: 25, 1925.
- c. Kunstler, M.: The Pertussis Skin Test in the Newborn and Later Infancy, *Canad. M. A. J.* 52: 63, 1945.
32. Gellhorn, A.: Placental Transmission of Radioactive Isotopes, *Proc. Conf. Probl. Human Fertil.*, p. 158, 1943.
33. a. Mishulow, L., et al.: Stimulation of Pertussis Protective Antibodies by Vaccination, *Am. J. Dis. Child.* 62: 1205, 1941.
- b. Weichsel, M., Rubin, H. J., Cohen, P., and Lapin, J. H.: Intracutaneous Tests With Pertussis Toxin in Complement Fixation Tests in Whooping Cough, *Am. J. Dis. Child.* 60: 862, 1940.
34. Longworth, L. G., Curtis, R. M., and Pembroke, R.: Electrophoretic Analysis of Maternal and Fetal Plasma and Sera, *J. Clin. Invest.* 24: 46, 1945.

35. a. Freund, J.: Influence of Age Upon Antibody Formation, *J. Immunol.* 18: 315, 1930.  
b. Baumgartner, L.: Age and Antibody Production: *J. Immunol.* 27: 407, 1934.
36. a. Sauer, L. W.: Age Factor in Active Immunization Against Whooping Cough, *Am. J. Path.* 17: 719, 1941.  
b. Sutliff, W., and Finland, M.: Antipneumococcic Reactions in Individuals of Different Ages, *J. Exper. Med.* 55: 837, 1932.
37. a. Dyer, R. E.: Role of Active Immunization in Advances of Medicine, *Proc. Am. Philosoph. Society* 88: 182, 1944.  
b. Dyer, R. E.: Committee on Administrative Practices, Dr. Haven Emerson, Chairman: Multiple Antigens for Active Immunization, *Am. J. Pub. Health* 34: 452, 1944.
38. a. Wiener, A. S., and Sonn, E. B.: Pathogenesis of Congenital Hemolytic Disease, *Am. J. Dis. Child.* 71: 27, 1946.  
b. Wiener, A. S.: Competition of Antigens in Isoimmunization of Pregnancy, *Proc. Soc. Exper. Biol. & Med.* 58: 133, 1945.

1175 PARK AVENUE.

993 PARK AVENUE.

# AN EPIDEMIC OF DIARRHEA IN THE NEWBORN NURSERY CAUSED BY A MILK-BORNE EPIDEMIC IN THE COMMUNITY

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TOPEKA, KAN.

**I**N AN epidemic of diarrhea in the newborn nursery, too often the first thought is to close the obstetric floor. It is the purpose of this article to present a nursery epidemic which was secondary to a milk-borne epidemic of diarrhea in the community. From the results it would seem advisable to consider that a disease in the community may be the possible source of a nursery infection.

On Oct. 1, 1945, Dr. M. O. Steffen, at Great Bend, Kan., reported to the Kansas State Board of Health some deaths of infants in the newborn nursery at St. Rose Hospital. A preliminary investigation revealed that there had been occurrences and recurrences of diarrhea in the nursery and in infants dismissed from the nursery since June. It was also determined that there had been several cases of diarrhea in the community and neighboring communities for several months. Because of the possibility of a common source for this diarrhea, a more detailed study was conducted.

There were twenty-four infants who had either developed this disease in the hospital nursery or had developed it after leaving the nursery and then had returned to the hospital. Of these twenty-four infants, nine died. During this period of time there had been 278 births in the hospital. This paper deals with these twenty-four cases, referring to the community study only where it has a bearing on the hospital study.

Fifteen infants developed symptoms in the nursery, while nine had been discharged from the hospital and returned. Of these nine infants, seven had the history of contact with a case of gastroenteritis at home; one (Case 11) returned to the pediatric ward because of a feeding difficulty, and seven days after admission, developed diarrhea simultaneously with the development of several cases in the nursery. The ninth infant (Case 23) developed symptoms the very day he left the hospital, so we can conclude that he contracted the disease there. The mother of one patient (Case 19) developed gastroenteritis in the hospital, although the infant did not develop the disease until two days after discharge. In Case 18 the histories given by the family varied. One gave the first day after discharge from the hospital as the day of onset; the other gave the fifth day. On the second day after discharge, a member of the household developed diarrhea and subsequently two other members, before the infant returned to the hospital on the eighth day. All three cases (Cases 18, 19, and 23) were recorded on Chart 2. A total of nineteen probably contracted the disease in the hospital. It can be seen from Chart 1 that several infants developed symptoms shortly after leaving the hospital, so it is possible that they contracted the disease there or at home.

\*Director, Division of Maternal and Child Health.

†Director, Public Health Laboratories, Kansas State Board of Health.

Diarrhea was the first, and often the only symptom, which might vary from a few soft frequent stools to extremely watery ones. The next most common symptom was vomiting, then dehydration, cyanosis, collapse, pain, and fever, in that order. In three infants who died, early and extreme setting of the muscles in rigor mortis occurred. In many of these cases, the diarrhea seemed to be recurrent over periods of time as long as six weeks, just as it was in some of the adult cases. The incubation period of the disease varies from one to seven days, most commonly six. In only one case was the onset less than 4 days after birth; the onset in this case was 3 days. The average age at death was  $25\frac{1}{4}$  days; the range was 11 to 54 days. The average number of days between onset and death was  $16\frac{1}{2}$  days; the range was 4 to 38.

It seems logical to divide this study into three parts: epidemiological, milk sanitation, and bacteriologic.

#### EPIDEMIOLOGICAL

The science of epidemiology is older than the science of bacteriology; in fact, at least one classical epidemiological study was made before the advent of bacteriology. The epidemic study in this case should be based upon the knowledge of the method of spread of gastrointestinal diseases rather than upon the specific organism.

From the Charts 1 and 2, these points can be noted:

1. There were six outbreaks in the nursery, with the development of from one to six cases in each outbreak.

2. These outbreaks were separated by periods of 15, 7, 49, 31, and 10 days. It would seem impossible for the infection to have been maintained by passage from infant to infant or through fomites; it must have been reintroduced.

3. There were no secondary cases occurring in the nursery, with the possible exception of the August outbreak.

4. Prior to every outbreak in the nursery, except the one in August, one mother or nurse on the obstetric floor developed the disease. In the August and October outbreaks, mothers had had the disease shortly before entering the hospital. In August, the second case (Case 15) appears to be secondary to Case 14, the infant of one of these mothers.

5. In every case where the mother had had the disease, her infant developed it.

6. One case (Case 11) occurred in the pediatric ward (farthest removed from the nursery) simultaneously with the late June outbreak in the nursery.

7. One mother (Case 16), who did not have diarrhea, came from a family in which two children did.

In addition to the information shown on the chart, several cases of gastroenteritis developed in other parts of the hospital, in medical and surgical patients, and in twenty-four nurses and nuns.

The hospital nursery had been very crowded, of necessity housing three times the number of infants it was built to accommodate. A proportionately large number of premature infants was in the nursery. A shortage of profes-



sional personnel existed. Such conditions resulted in some breaks in technique, but they were not gross breaks and they would not explain the epidemic.

But the nursery outbreaks can easily be explained on the basis of secondary infection from infected mothers or nurses if we keep in mind a well-known fact in the epidemiology of gastrointestinal diseases, namely, that apparently healthy persons who have ingested organisms are carriers of those organisms until they are eliminated from the alimentary canal. These organisms may be eliminated in one or two days. Nevertheless, until they are eliminated, persons harboring them are temporary carriers, capable of passing the infection on to others. The only condition which would result in a large group of temporary carriers is a recent ingestion of a contaminated food or water.

Since one mother or nurse, or both, developed the disease prior to every outbreak, it shows that there was repeated ingestion of contaminated food or water and that there was an opportunity for others, who were not sick, to become temporary carriers. This is demonstrated in the case of the infant (Case 16) whose mother, apparently well, came from a family where other members had diarrhea when the mother was admitted to the hospital.

Each infant infected in the hospital was secondarily infected from his mother or from a nurse who had received the infection from contaminated food or water. Likewise, each individual infected at home was secondarily infected by a member of the family who had, in most instances, not eaten food at the hospital.

In addition, there were several hundred cases of diarrhea occurring in the community (histories were obtained on more than 400 which occurred between July 1 and October 15) and several cases occurred in outlying communities. The hospital, the city, and the outlying communities had separate water supplies.

The only foods common to the hospital and city which were not cooked before use in the hospital were bread, lettuce, cold meats, and milk. The only persons who developed diarrhea in the outlying communities were persons who had been using milk from the dairy at Great Bend, which supplied the hospital. Only twenty-one of the twenty-four mothers could be contacted, but the one food that all twenty-one used at the hospital was milk. Two of these mothers developed diarrhea before entering the hospital, but they bought milk from the same dairy.

From an epidemiological standpoint, a contaminated milk supply, which had not been adequately cleaned up over a long period of time, was a source of the infection. It could account for the epidemic in Great Bend, the cases in the outlying communities, the cases among patients in the hospital, among nurses and nuns (many of whom had not eaten food away from the hospital for months), and for the outbreaks among the infants in the hospital. All of these cases cannot be explained in any other way.

#### MILK SANITATION

Milk for 90 per cent of the community came from two dairies which supposedly sold pasteurized milk. Inspection revealed both to be filthy, filled

with flies, to have dogs in the milk room, to lack handwashing facilities, to have dust blowing in, to have no recording thermometers on the pasteurizing vats, and in one dairy a rag had been tied over a leak in a water pipe directly over the cooling coils. From this rag, water dripped into the pasteurized milk. The cleaning and sterilizing of bottles was so carelessly done that in the exchange of bottles, an infection in one dairy could easily spread to the other. A heavy collection of milkstone on the pipes testified to the fact that they had not been properly cleaned for months.

The phosphatase tests on milk from both dairies showed that the milk had not been pasteurized. Bacterial counts on the milk from both dairies were over three million per cubic centimeter. Further bacterial studies on the milk will be included under the next heading.

#### BACTERIOLOGIC

The bacteriologic study of the cause of illness and death of infants in the St. Rose Hospital, Great Bend, was started on Oct. 1, 1945. A complete laboratory was set up in the hospital and three bacteriologists from the State Public Health Laboratories were assigned to study this epidemic. Stool specimens were obtained from all sick and some normal infants; from hospital nurses and employees; from mothers, and from residents of Great Bend who were sick or had recently been sick. Rectal swabs were used to collect the specimens except in cases of the infants. The stools were plated directly on SS agar, MacConkey's agar, and desoxycholate agar. Tetrathionate broth and Selenite F broth were used as enrichment media. All suspicious colonies were removed and placed in Kligler iron agar. These cultures were then sent to the Central Public Health Laboratories, Topeka, where complete study and identification was made.

Because of the clinical symptoms of the disease in some infants, and the history of a sick father who returned by airplane from overseas, efforts were made to isolate all types of organisms, even *Vibrio comma*. Although *Pseudomonas aeruginosa* was isolated from the first case seen on October 1, it was difficult to believe this was the etiological agent, therefore, every effort was used to eliminate all other possible organisms. Streptococci, both aerobic and anaerobic, were looked for in addition to the afore-mentioned groups of organisms. More than 500 stool specimens were examined.

A brief summary of the findings on stool specimens is given in Table I.

In addition to the results already given, a large number of Proteus and Salmonella-like cultures, which are, for the present, being classified in the paracolon group, were isolated. More than 700 cultures were studied. The identification consisted of cultural, biochemical, and typing for antigenic characteristics.

It is interesting to note that nurses in the nursery and pediatric departments were carriers of *Ps. aeruginosa*. Another finding of interest was the isolation of *E. typhosa* from one of the nurses.

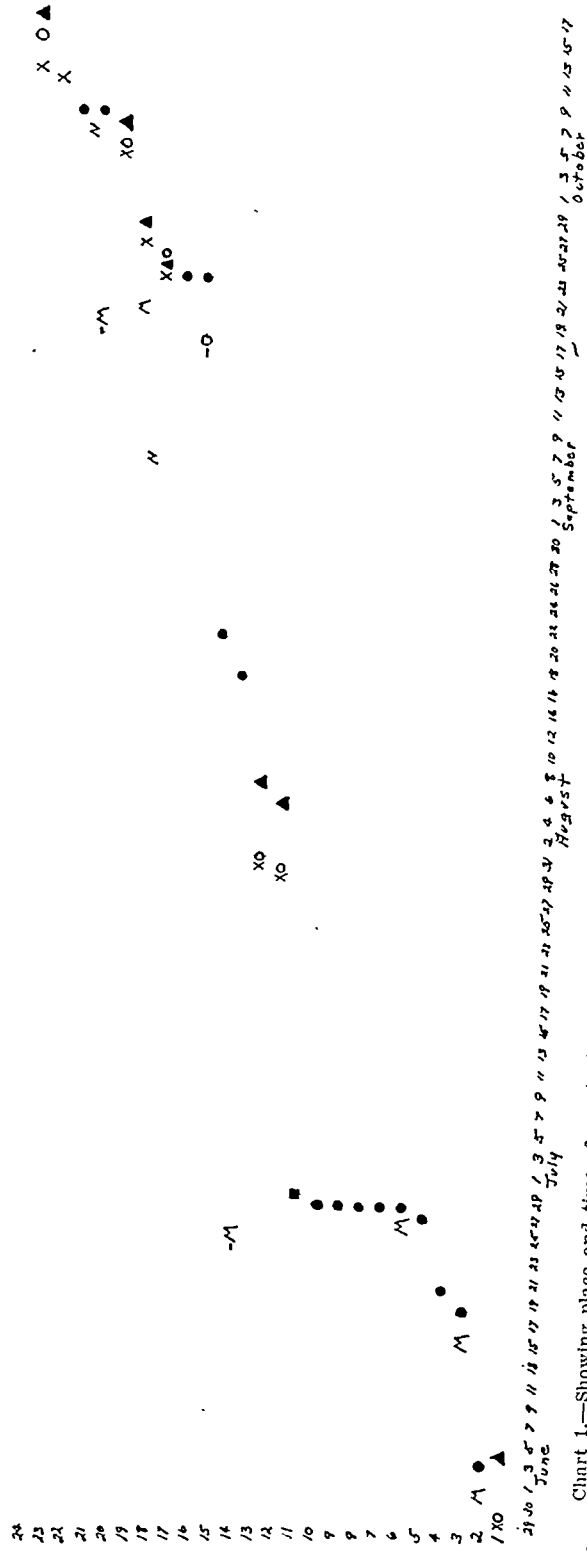


Chart 1.—Showing place and time of onset of symptoms and probable source of infection. The solid figures represent onsets which were on the dates corresponding to the vertical lines.

● Onset in the nursery.

■ Onset in pediatrics.

▲ Onset at home.

X Represents date of dismissal from hospital of those who were dismissed and then returned.

The letters represent the date of onset in cases which were probable sources of infection for the infants except in cases of other family mem-

bers where this represents the date the infant came in contact with them.

M Mothers who developed diarrhea in the hospital.

-M Mothers who developed diarrhea before entering.

N Nurses on the obstetric floor who developed diarrhea.

O Other members of the family with diarrhea when infant returned home.

-O Other members of the family who had diarrhea at the time the mother entered the hospital.

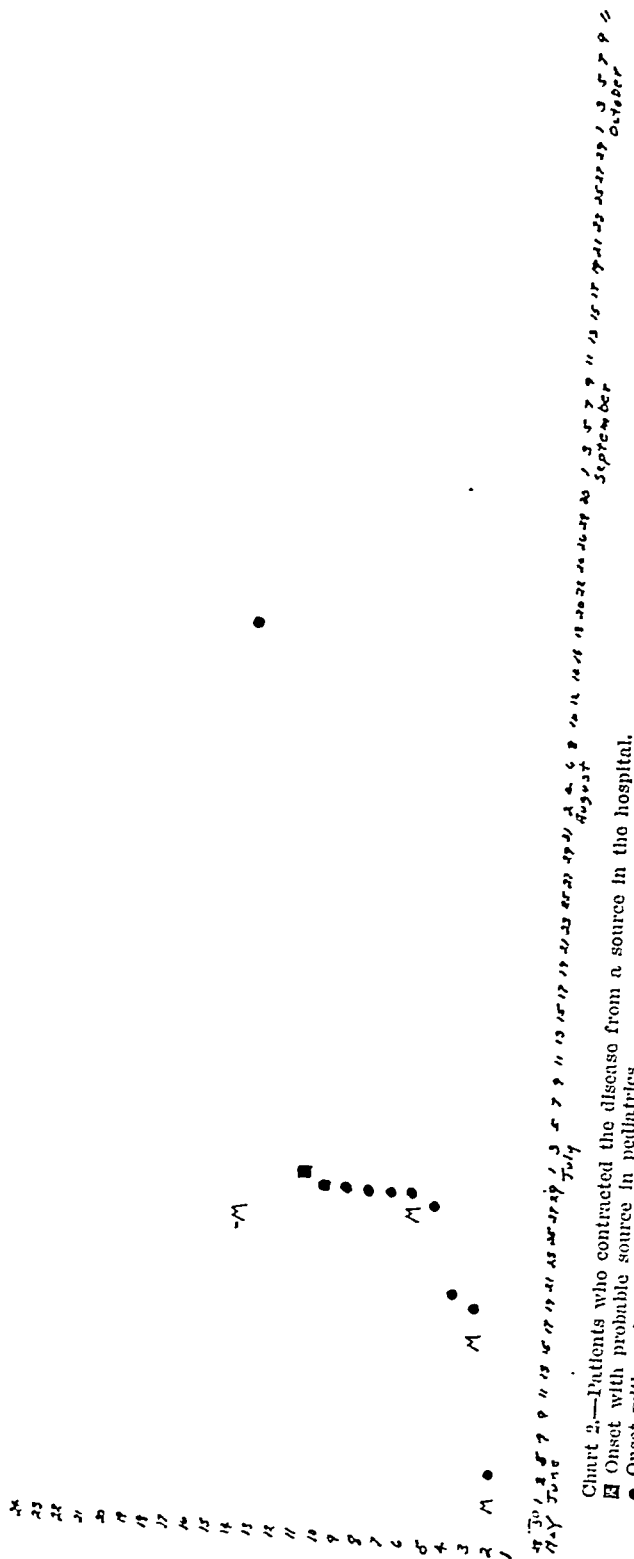


Chart 2.—Patients who contracted the disease from a source in the hospital.  
 ■ Onset with probable source in pediatrics.  
 ● Onset with probable source in the nursery.

No figure is shown for dismissal from the hospital. Otherwise the legend is the same as in Chart 1.

TABLE I

A. Number of infants (under 2 years of age) studied bacteriologically	38
<i>Ps. aeruginosa</i> isolated	24
B. Number of infants followed clinically in this study	24
Number above infants studied bacteriologically	9
<i>Ps. aeruginosa</i> isolated	9
C. Number normal infants studied bacteriologically	13
<i>Ps. aeruginosa</i> isolated*	5
D. Autopsies on infants	2
<i>Ps. aeruginosa</i> isolated (liver, spleen, gall bladder, intestines)	2
E. Rectal swabs on nurses and employees in hospital	103
<i>Ps. aeruginosa</i> isolated	16
<i>Eberthella typhosa</i> isolated	1
<i>Shigella alcalescens</i> isolated	2

\*Four of the 5 infants became sick later. The mother of the fifth infant developed diarrhea at the time of dismissal from the hospital. Due to discontinuance of public health nursing services, this infant could not be followed.

**Water Supply.**—There were three different sources of water for the community: hospital, city, and private wells. The hospital had its own water supply and bacteriologic examinations showed the water to be free of coliform organisms and *Ps. aeruginosa*.

The city water supply (17 samples) did not show the presence of coliform or *Ps. aeruginosa*. It is chlorinated continuously and tested regularly under the supervision of the State Board of Health. It is estimated that there are some, 1,300 private water supplies in Great Bend. Upon inspection by the sanitary engineers, none was found cross connected to the city water. Seventy-two samples of water from private wells were examined and coliform organisms found in sixteen of them. *Ps. aeruginosa* was isolated from four wells.

**Milk Supply.**—The milk sanitarians collected many samples, raw and pasteurized, at the plants and at the time of delivery, and brought them to the laboratory for examination. The bacteriologic examinations consisted of the standard plate count, microscopic examination, coliform determinations, and phosphatase tests. A summary of the results is given in Tables II and III.

TABLE II

DAIRIES	NUMBER	PER CENT OF TOTAL VOLUME OF MILK
Pasteurized	3	80.5
Raw	6	19.5

TABLE III

MILK SPECIMENS	STANDARD PLATE COUNT			COLIFORM		PHOSPHATASE TEST			
	NO. OVER 10,000	NO. OVER 100,000	NO. OVER 3,000,000	NO. TESTED	NO. +	NO. TESTED	NO. +	NO. ±	NO. -
Pasteurized	38	28	8	30	23	64	9	14	41
Raw	19	14	2						

The bacteriologic analysis of the milk showed that more than 22 per cent of the samples of Pasteurized Milk No. 1 had a standard plate count of over 3,000,000. Pasteurized Milk No. 2 had an average standard plate count of 110,000, and Pasteurized Milk No. 3 an average of 95,000.

The phosphatase tests showed that 7 per cent of the samples of Pasteurized Milk No. 1 was insufficiently pasteurized; 23 per cent of the samples of Pasteurized Milk No. 2 was not sufficiently pasteurized.

*Ps. aeruginosa* was isolated from the water running from the dirty rag which hung over the cooler into the milk.

#### TREATMENT

The treatment, before isolation of the organism, had consisted of penicillin, transfusions, parenteral fluids, and sulfonamides; the last two were the most effective. Following isolation of the organism, a review of the literature revealed that it produced small amounts of hydrocyanic acids. It was conceivable that the symptoms could be attributed to slow poisoning from this source. Proceeding upon this assumption, methylene blue, which had often been used effectively in this type of poisoning, was suggested as a treatment. Dr. Steffen used it and reported miraculous results with clearing of cyanosis and signs of toxicity in less than ten minutes. This affords a therapeutic test which supports the rest of the work.

#### MEASURES TAKEN TO STOP THE EPIDEMIC

1. The hospital autoclaved all milk until a safe milk supply could be obtained.

2. Whenever possible, stool cultures were made on mothers two weeks before they entered the hospital. Upon entry, another stool culture was made and the mothers were questioned concerning a history of diarrhea.

3. Whenever a positive stool culture was obtained, or the mother had a history of diarrhea within the past two weeks, or developed diarrhea on the obstetric floor, she was isolated on a separate floor and the infant was taken from the nursery and also isolated from the mother. If a history of diarrhea or a positive stool culture was obtained before entrance, the mother was delivered in her own room.

4. When an infant developed the first suspicious sign of diarrhea, the mother and infant were isolated and the physician notified so that treatment might be started on the infant.

5. Another room was set up for a nursery and all new infants placed in this room until all the infants in the original nursery had been discharged and the nursery could be thoroughly cleaned.

6. All mothers and infants were sent home on the fourth day routinely. The public health nurse was notified when the mother and infant were dismissed from the hospital so that a visit could be made to give the mother instructions on the care of the baby and techniques which should be used to prevent infection. If on the fourth day, the infant showed signs of diarrhea, he was sent to the pediatric department rather than home. If for some reason the mother or infant had to stay in the hospital more than four days, the mother and infant were placed in a private room and the infant kept out of the nursery.

7. Public health nurses were assigned to assist mothers leaving the hospital with newborn infants in putting into practice every precaution to safe-

guard infants from infection. Services rendered while in the home were: formula preparation; bathing; care and feeding of the infant; care of the mother while in bed; and general instructions to members of the family regarding prevention of disease. Public health nurses continued helping mothers in caring for all newborn infants until the epidemic had nearly subsided.

8. Stool cultures were repeated on all nurses in the nursery and pending report, all nurses who had had diarrhea in the past month were removed from the nursery.

The epidemic subsided within three weeks after these measures had been put into effect.

#### SUMMARY

1. This is a report of an epidemic of diarrhea in twenty-four newborn infants in which there were nine deaths. Eighteen of these infants probably contracted the disease in the newborn nursery. One who was discharged returned to the hospital as a feeding problem and developed diarrhea seven days later. Five developed diarrhea at home after being in contact with a case in the family.

2. The infecting organism was *Ps. aeruginosa* which gained entrance to the milk supply through a rag which was dripping into the pasteurized milk of one dairy. Bottles of dairies were exchanged without proper cleaning and sterilization, so that the organisms easily gained access to the other dairies.

3. The contaminated milk caused an epidemic of gastroenteritis in Great Bend, Kan., and caused outbreaks among patients and employees of the hospital and in consumers of the Great Bend milk in outlying towns.

4. The infants were secondarily infected by mothers and nurses who drank the milk in the hospital or by other members of the family after the infants had been dismissed from the hospital.

5. Apparently well persons who had ingested the contaminated milk acted as temporary carriers, capable of passing on the organism until they had eliminated it from the alimentary canal.

6. Of twenty-four infants studied clinically, it was possible to study nine bacteriologically. *Ps. aeruginosa* was isolated in the stools of all of the nine. Autopsy material was obtained from two cases for bacteriologic study and *Ps. aeruginosa* was isolated from both.

7. Epidemiological, milk sanitation, and bacteriologic studies, all support this conclusion, which is further supported by the therapeutic results of methylene blue.

8. The epidemic subsided within three weeks after control measures based upon the findings were put into effect.

## THE EFFECT OF SALICYLATE ADMINISTRATION ON THE PROTHROMBIN TIME

CLIFTON D. GOVAN, JR., M.D.

THE prothrombin deficiency which occurs following the administration of salicylates was first demonstrated in rats by Link and his associates.<sup>1</sup> They suggested their findings be explained on the basis that both the salicylate compounds and the anticoagulant dicumarol liberate salicylic acid in the body which lowers the prothrombin content. Although Hanzlik<sup>2</sup> by in vitro experiments was unable to demonstrate the liberation of salicylic acid from salicylate compounds, later studies<sup>3-5</sup> confirmed Link's observations on the prothrombin changes by demonstrating a hypoprothrombinemia in man following the administration of salicylates. Among these studies, those of Fashena and Walker<sup>5</sup> showed the salicylate compounds tended to produce their maximum effect upon the prothrombin activity on the second day of ingestion and thereafter less and less effect was apparent despite continued therapy. Although in no instance was a normal pretreatment level of prothrombin activity reached in none of the studies were the prothrombin changes followed by periods longer than eleven days. For these reasons, a study of the prothrombin activity in patients receiving therapeutic doses of salicylates for long periods was undertaken.

In this study, an attempt was also made to correlate the changes in the prothrombin activity with the serum levels of salicylate and to determine whether the administration of salicylate compounds produced changes in the alkali reserve, blood and urine pH, respiratory rate, and urine.

### METHODS

*Subjects.*—Twenty-four patients were included in this study. The patients ranged in age from 4 months to 11 years. Eleven were infants and thirteen were children. The ages and condition of the patients at the time the studies were begun are seen in Chart 1. No patient had received any form of salicylate medication for three weeks prior to the observation, and no other form of medication for one week prior to the study. All the subjects (except Cases 12 and 21) had received the general ward diet for at least two weeks before the beginning of the investigation.

*Procedure.*—On each patient, control determinations of the prothrombin time, carbon dioxide combining power, and blood and urine pH were obtained, preceding the oral administration of the salicylate. The patients were divided into groups of three. Nine infants and nine children received acetylsalicylic acid and two infants and four children received sodium salicylate. The patients in Groups 1, 2, and 3 were infants and those in Groups 4, 5, 6, and 8 were children.

From the Department of Pediatrics of Johns Hopkins University School of Medicine and the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.



Group 7 consisted of two infants and one child. Chart 2 shows the initial oral dose and form of salicylate compound received by each group. All patients who received initially less than 2 grains per pound of body weight per day were given, at four-day intervals, 0.5 grain per pound per day increase in medication until their limit of tolerance was reached. To six patients (Cases 10, 11, 12, 13, 14, and 15) on the seventeenth day of salicylate medication varying amounts of sodium bicarbonate were given simultaneously with the salicylate.

Following the initial dose of salicylate, determinations of the prothrombin time, carbon dioxide combining power, blood and urine pH, and plasma salicylate levels were performed every second, third, or fourth day during the time salicylates were being administered. These determinations were repeated the second and fourth day following cessation of medication. Urine was examined daily for pH, presence or reducing substance and albumin.

CASE	AGE	CONDITION AT ONSET OF STUDY
1	20 months	Well
2	7 months	Well
3	24 months	Well
4	11 months	Well
5	24 months	Well
6	4 months	Well
7	18 months	Well
8	19 months	Well
9	18 months	Well
10	9 years	Well
11	11 years	Acute rheumatic fever
12	3 years	Acute rheumatic fever
13	6 years	Acute hemorrhagic nephritis
14	9 years	Acute hemorrhagic nephritis
15	6 years	Acute hemorrhagic nephritis
16	6 years	Well
17	5 years	Well
18	4 years	Well
19	18 months	Well
20	19 months	Well
21	11 years	Acute rheumatic fever
22	11 years	Well
23	11 years	Well
24	10 years	Well

Chart 1.

In order to determine the effect on the prothrombin time, three patients (Cases 16, 17, and 18) were given 2 mg. of hykinone daily during the whole period of observation.

*Prothrombin Test.*—The prothrombin time was determined by Smith's bedside test,<sup>6</sup> a modification of Quick's method.<sup>7</sup> Desiccated rabbit's brain thromboplastin which had been stored in vacuo was used. Each determination was made using glass tubes especially cleaned and dried. A normal prothrombin time was performed with each determination. The normal controls consisted of four healthy adult interns who alternated as controls during the period of observation. For a further check of the normal variations in the prothrombin time a determination of the prothrombin time was made every three days for one

month on a mentally retarded but otherwise normal patient. A control prothrombin time was performed with each determination as described.

The prothrombin activity as determined using the following formula:

$$\frac{\text{Prothrombin activity}}{\text{or Clotting activity}} = \frac{\text{clotting time of normal control}}{\text{clotting time of patient}} \times 100$$

For example, a patient's blood clotted in 40 seconds, a control's in 20. The prothrombin activity, therefore, was 50 per cent of normal. According to Smith and his associates<sup>6</sup> a clotting activity between 40 and 70 per cent is definitely in the danger zone.

The carbon dioxide combining power was determined by the Van Slyke manometric technique.<sup>5</sup>

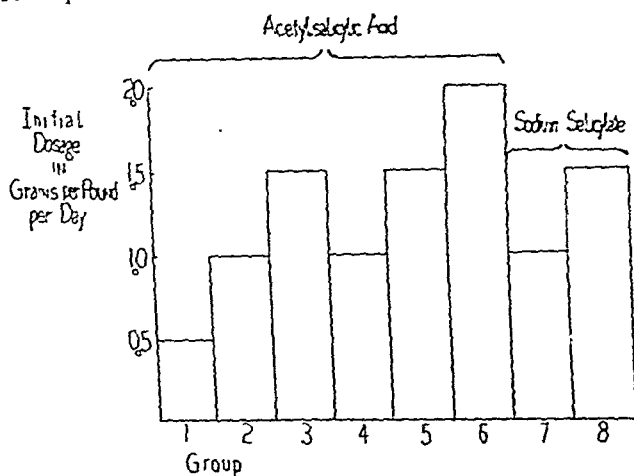


Chart 2.—Initial oral dose and form of salicylate compound received by each group.

The blood pH was determined by a colorimetric method, using phosphate buffers. The method was standardized with hydrogen electrode pH determinations. The urine pH was determined by the use of nitrazine paper.

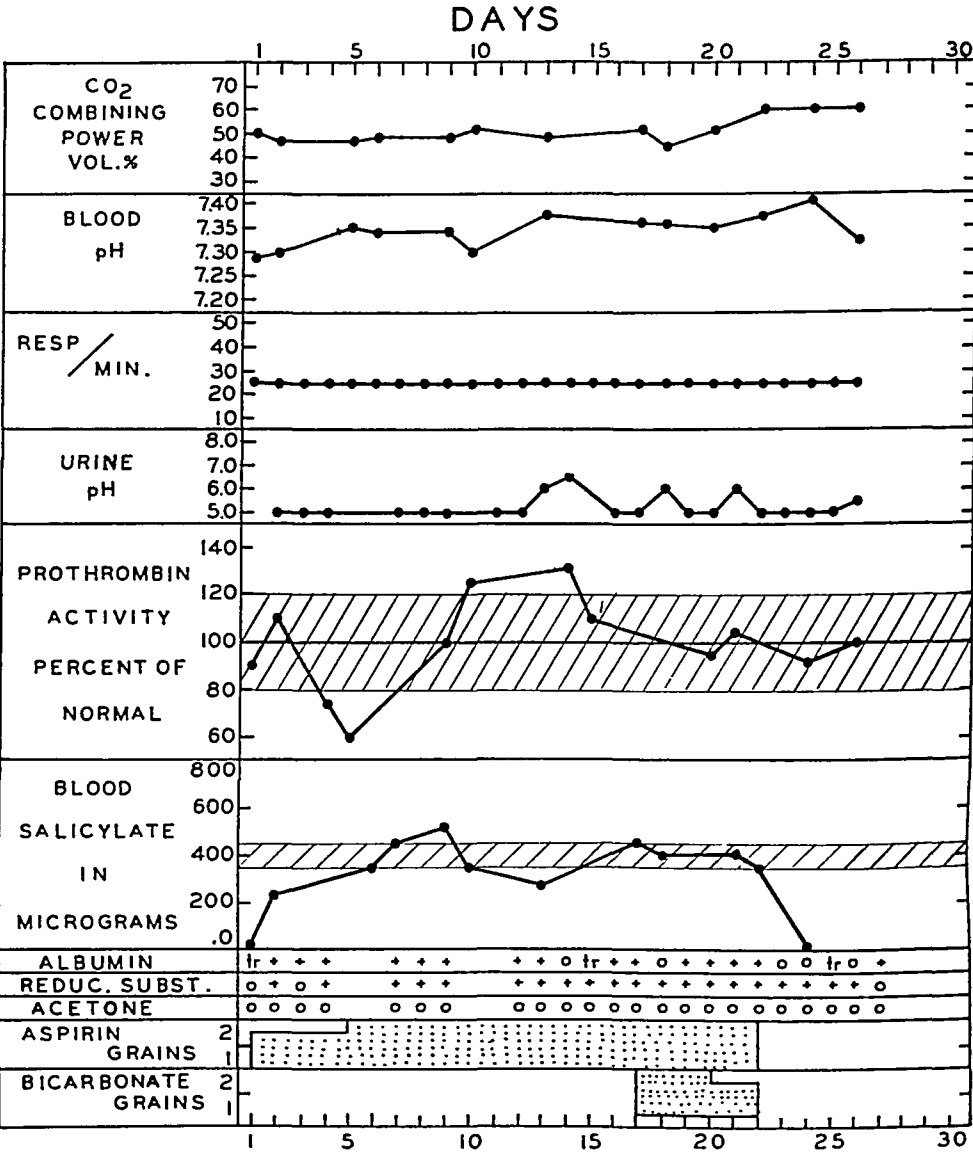
Reducing substance found in the urine of patients receiving salicylates was roughly estimated by the standard Benedict qualitative test.

The plasma salicylate levels were determined by the method of Brodie, Udenfriend, and Coburn,<sup>9</sup> using 1 to 2 c.c. of serum for each determination.

#### OBSERVATIONS

(Charts 3 and 4)

*Prothrombin Activity.*—The prothrombin activity of the mentally retarded but otherwise normal patient showed a marked variation from day to day but at no time fell below 80 per cent of normal. During the period of observation, six, or approximately 25 per cent, of the patients showed an abnormal prolongation of the prothrombin time, i.e., reduction of the prothrombin activity. The most marked hypoprothrombinemia occurred between the second and fifth day



B.A.P. 6 YRS No 13      DAYS

Chart 3.—This chart represents one of the six patients showing an abnormal prolongation of the prothrombin activity.

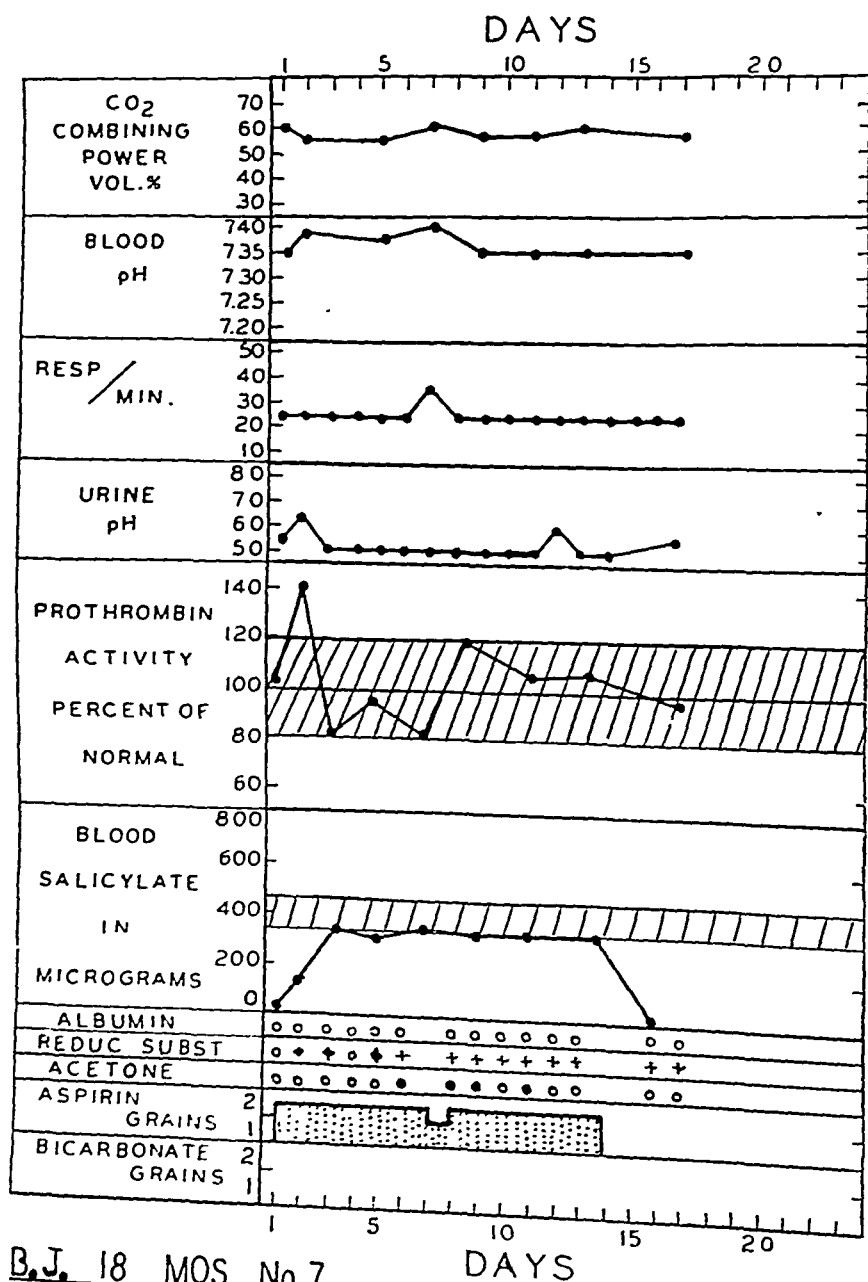


Chart 4.—This chart represents one of the eighteen patients showing no abnormal prolongation of the prothrombin activity.

of medication. In each of the six patients normal pretreatment levels of prothrombin activity were reached by the ninth day of continuous salicylate administration.

No correlation was observed between the blood salicylate levels and prothrombin time. Reduction of prothrombin activity was observed even with blood salicylate levels as low as 100 microgammas.

No difference in the effect on the clotting mechanism was observed between cases in which a sudden elevation of blood salicylate level occurred and those patients in which a gradual rise in blood salicylate level was produced.

Salicylates apparently affected, in a similar manner, the prothrombin activity in both infants and children.

It is of interest and in accord with the recent findings of Shapiro<sup>10</sup> and Meyer and Howard<sup>3</sup> that no changes in the prothrombin activity occurred in those patients receiving vitamin K.

*Blood Salicylate Level.*—The blood salicylate levels as determined in infants depended on the manner in which the drug was offered. High levels in the blood were more easily attained in infants when sodium salicylate in solution was given. To attain so-called therapeutic levels of blood salicylate in infants and children, doses between 1.5 and 2 grains per pound per day were required.

In most instances, blood salicylate levels were not measurable forty-eight hours after withholding salicylate medication.

Sodium bicarbonate when given in equal dosage with salicylates tended to lower the blood salicylate levels, but the striking depression as noted by Smull and her co-workers<sup>11</sup> was not observed.

*Urinary Findings.*—The urine pH revealed a tendency to shift toward the acid side, but no constancy was noted. In most instances a reducing substance was present in the urine by the second day of salicylate ingestion. On several occasions reduction of cupric sulfate to red cuprous oxide was observed. The reducing substance is thought to be a glucuronide.<sup>5</sup> Examination of the urine for acetone, using the Rothera test, revealed no acetone in any specimen. The presence of albumin was frequently noted, being a more common finding in the nephritic subjects.

*Salicylate Intoxication.*—During this study six patients developed signs of intoxication resulting from the administration of salicylates. Four were infants and two were children. Five of the six patients who developed toxic signs on salicylate therapy without bicarbonate had a slight elevation of the blood pH. In one patient no change in the pH was apparent. The signs of intoxication were not allowed to progress longer than eight hours. The signs in the order of their appearance were: (1) hyperpnea, (2) apathy, (3) anorexia, (4) vomiting, (5) fever. The patient in whom the signs appeared the most severe had blood salicylate levels far below the so-called therapeutic level. Other symptoms included vague abdominal pains and muscle pains.

#### DISCUSSION

The prothrombin deficiency attending the therapeutic administration of salicylate compounds is apparently neither a constant nor a dangerous feature

of this form of medication. When salicylate compounds produce a depression of the prothrombin activity, it is usually between the second and fifth day of administration of the drug and by the ninth day has usually returned to normal.

The mechanism by which salicylate compounds produce a hypoprothrombinemia is obscure. It is unlikely that the hypoprothrombinemia results from a direct action of the salicylates on the circulating prothrombin, for if such were the case the effect would be constant and dependent on the concentration of salicylates in the extracellular fluids. The observations in this study did not favor this view. It seems more likely that the depression of the prothrombin formation is a result of changes in the liver. It is well known that salicylates in very high concentrations can produce histologic changes in the livers of experimental animals. It would be anticipated therefore that similar lesions would occur in man and the degree of damage would be dependent on the concentration of salicylate in the body. Thus, if it can be assumed that the depression of prothrombin activity represents a form of liver damage, the effect of therapeutic concentrations of salicylates in the body upon the liver must be minimal. This is evidenced by the following: (1) Prothrombin deficiency does not always follow the administration of salicylates; (2) when the prothrombin activity is depressed it spontaneously returns to normal; and (3) hykinone or vitamin K will prevent a reduction of the prothrombin content.

There have been several reports of hemorrhagic complications arising during the administration of salicylates, and it is likely that hypoprothrombinemia constitutes one of the mechanisms by which this effect is produced. As has been pointed out, however, if the prothrombin activity is dependent on the amount of liver damage produced by the salicylates, it would be correct to assume that in individuals accidentally poisoned with salicylates the high concentrations would be more likely to produce hypoprothrombinemia and hemorrhages. It is in this type of patient that intensive vitamin K therapy would be indicated. However, as Link and associates<sup>1</sup> have pointed out, prothrombin deficiency alone does not explain the hemorrhages. It is likely, however, that vascular trauma and dilatation plus prothrombin deficiency play a part in some patients in the production of hemorrhages.

#### SUMMARY

1. Varying doses of salicylate were administered to twenty-four patients (eleven infants and thirteen children) over periods of fifteen to thirty-five days.
2. Eighteen patients received acetylsalicylic acid and six patients received sodium salicylate.
3. Determinations of the prothrombin time, carbon dioxide combining power, blood and urine pH, and plasma salicylate levels were made every second, third, or fourth day during the period of observation.
4. Six patients showed an abnormal prolongation of their prothrombin time or reduction of their prothrombin activity.
5. The most marked reduction of the prothrombin activity occurred between the second and fifth day of salicylate administration. In every patient, despite

continuous salicylate therapy, the prothrombin activity returned to normal by the ninth day of medication.

6. Six patients showed early signs of salicylate intoxication, during which time a slight elevation of the blood pH occurred in five. Intoxication occurred in one patient with salicylate levels as low as 100 microgammas.

7. No correlation was observed between the changes in the alkali reserve and serum levels of salicylate.

#### REFERENCES

1. Link, K. P., Overman, R. S., Sullivan, W. R., Nuebner, C. F., and Scheel, L. D.: Studies on Hemorrhagic Sweet Clover Disease, *J. Biol. Chem.* 147: 463, 1943.
2. Hanzlik, P. J.: Liberation of Free Salicylic Acid From Salicylate in Circulation, *J. Pharmacol. & Exper. Therap.* 17: 385, 1921.
3. Meyer, O. O., and Howard, B.: Production of Hypoprothrombinemia and Hypocoagulability of Blood with Salicylates, *Proc. Soc. Exper. Biol. & Med.* 53: 234, 1943.
4. Shapiro, S., Redish, M. H., and Campbell, H. A.: The Prothrombinopenic Effect of Salicylate in Man, *Proc. Soc. Exper. Biol. & Med.* 53: 251, 1943.
5. Fashena, G. T., and Walker, J. N.: Salicylate Intoxication, *Am. J. Dis. Child.* 68: 369, 1944.
6. Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R.: Clinical and Experimental Studies on Vitamin K, *J. A. M. A.* 113: 380, 1939.
7. Quick, A. J.: Prothrombin in Hemophilia and in Obstructive Jaundice, *J. Biol. Chem.* 109: 73, 1935.
8. Van Slyke, D. D., and Neill, J. M.: Determinations of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* 61: 523, 1924.
9. Brodie, B. B., Udenfriend, S., and Coburn, A. P.: Determination of Salicylic Acid in Plasma, *J. Pharmacol. & Exper. Therap.* 80: 114, 1944.
10. Shapiro, S.: Studies on Prothrombin, *J. A. M. A.* 125: 546, 1943.
11. Smull, K., Wegria, R., and Leland, J.: The Effect of Sodium Bicarbonate on the Serum Salicylate Level, *J. A. M. A.* 125: 1173, 1944.

## ACID-ENZYME CONVERTED CORN SYRUP IN INFANT FEEDING

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THE purpose of this paper is to report practical experiences with an acid-enzyme corn syrup in infant feeding.\*

In acid-enzyme conversion, as the name implies, cornstarch is first hydrolyzed with acid and steam until the hydrolysis has progressed to approximately the same degree as that achieved in the usual acid conversion process. It is then exposed to an enzyme which splits the residual dextrines further into maltose and dextrose. The syrup end product of acid-enzyme conversion is rich in maltose and dextrose and low in dextrines as compared to the endproduct of the straight acid conversion.

Clinical observations have been made of 2,120 artificially fed infants (Table I). Syrup containing 10 per cent added sucrose was used. The infants came from various economic levels and were deemed representative of all phases of health, illness, and growth. Many were being reared in their own homes and reported regularly to feeding clinics or doctors' offices for supervision; many were being cared for in orphanages and nursing homes; some were sickly hospitalized infants; some were newborns, full-term and premature, being cared for in an obstetric nursery. Those in the hospital groups could be classed as special feeding problems being newborn, premature, undernourished, or sick with some serious ailment. The majority, however, were normal and healthy, and were kept on their carbohydrate-containing feedings through the changes and vicissitudes attendant upon the lives of all babies.

Of the well babies, approximately 90 per cent were given whole milk in one form or another—homogenized, plain pasteurized, boiled, unboiled, diluted, or undiluted; the rest were fed evaporated milk mixtures. The sick, newborn, and premature infants in the hospitals received a wider diversity of feedings. The feedings containing the acid-enzyme corn syrup were begun at the time of weaning, or on admission to the hospital, nursing home, or feeding clinic. For those infants above 2 months of age, 1 part of syrup was added usually to 20 parts of milk; for those under 2 months the syrup was given in stronger proportions, as 1 part to 15 of milk, or 1 to 12. The infants in the various groups were chosen on an unselected and random basis. The observations extended over a three-year period.

*Ease of Digestion.*—In these clinical trials the acid-enzyme corn syrup proved satisfactory as a carbohydrate supplement for infant feeding. All the

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\*The acid-enzyme corn syrup used in these studies was "Sweetose," manufactured by the A. E. Staley Manufacturing Company, Decatur, Illinois.



evidence indicated that it was efficiently digested and absorbed. The infants thrived and grew normally. In none of the groups was there any unusual prevalence of diarrhea, vomiting, colic, or other symptoms of gastrointestinal irritation. The small intestines and colon did not seem to be overly distended with gas. There were no attacks of hives, asthma, eczema, bloody stools, or other major manifestations of allergy attributable to the syrup.

Another index of ready digestibility was the failure of any transient disturbances to become manifest when some other form of carbohydrate supplement in the milk feeding mixture was abruptly replaced by acid-enzyme corn syrup. Most of the infants subjected to this sudden change in diet were sick infants undergoing hospitalization for some acute and serious illness. There were several hundred such instances.

TABLE I. DISTRIBUTION OF INFANTS IN THIS STUDY

	NUMBER	AGE RANGE	AVERAGE DURATION OF EXPERIMENTAL FEED- ING PERIOD (WEEKS)
Infants in orphanages	700	Birth to 12 months	20
Infants raised at home	800	2 weeks to 10 months	24
Hospitalized sick infants	200	2 weeks to 12 months	2
Full-term newborns in nursery	400	Birth to 2 weeks	2
Premature newborns in nursery	20	Birth to 8 weeks	4
Total	2,120	Birth to 12 months	16

*Effect on Stools.*—Acid-enzyme corn syrup was not laxative in the concentrations given. Most mothers and nurses reported that the daily number of stools diminished a little or remained unaltered when infants who had been receiving maltose-dextrin preparations or simple acid converted corn syrups were changed abruptly to acid-enzyme corn syrup. The stools were usually semi-formed, soft, of inoffensive odor, and nonirritating to the skin.

With twenty infants, it was thought necessary to change to a more laxative sugar in order to obtain correction for undesired constipation. Conversely, an approximately equal number of infants who had been exhibiting loose and irritating stools with other carbohydrates were described as being "improved" when acid-enzyme corn syrup was substituted.

*Prelacteal Feedings.*—More than 1,000 infants in the first few days of life were given boiled water containing 5 per cent acid-enzyme corn syrup. Such sweetened water proved to be well taken and gave rise to no gastrointestinal upsets.

*Convenience.*—Acid-enzyme corn syrup was found to be very readily soluble. Only a few minutes were required for it to go into solution even when the water or milk to which it was being added was ice cold. This quick solubility of acid-enzyme corn syrup was helpful in the preparation of feeding mixtures from unboiled, homogenized milk. With the ingredients kept cold, and the bottles permitted to grow cool before removal from the sterilizer, all manipulations of mixing and bottling could be done at refrigerator temperature.

This avoided the stimulation of bacterial growth which accompanies even a brief period of temporary warming.

#### SUMMARY

Milk feeding mixtures made with acid-enzyme corn syrup were fed to more than 2,000 infants of diverse ages and states of health and illness. The syrup proved highly satisfactory as a feeding supplement. It was palatable, non-laxative, nonallergenic, provoked no gastrointestinal distress, and appeared to be efficiently digested and absorbed.

Acknowledgment is hereby made of the cooperation of the following Philadelphia institutions in securing necessary data for this study: Sheltering Arms, Florence Crittenton Home, Salvation Army Home, Homewood School, St. Vincent's Hospital and Orphanage, Rodeph Shalom Well-Baby Clinic, University of Pennsylvania Hospital, Children's Hospital, Doctor's Hospital, and Presbyterian Hospital.

## SQUINT IN CHILDREN

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THE proper disposition of the child with an imbalance of the extraocular muscles is probably the most important ophthalmological problem facing the pediatrician. He is usually the first to see children with latent or obvious squint; and his responsibility does not end with their referral to an eye man. He should possess some understanding of the muscle imbalances, so that he may aid the child in securing proper care and cooperate in the giving of that care.

It is the important duty of the pediatrician to see that these youngsters do not go into adulthood untreated. At what age then should he refer these children to an eye man? In the stone age of ophthalmology the tendency was to wait in the hope that these youngsters would outgrow their "cross eyes." It is a fact that in a few cases the eyes do become straighter with advancing age, but the number is far too small to make waiting profitable. According to White, the child should be seen within two weeks after the squint is noted. Many children can be started on treatment almost immediately. Many will tolerate glasses at 18 months of age, or even less. It is well to bear in mind the fact that the macula lutea may not attain its full development until the child is about 4 months of age. All infants may periodically appear "cross eyed" before that period, as they do not have the ability to fuse images.

### ETIOLOGY

All of us, normally, tend to fuse in binocular single vision; that is, to see simultaneously with both eyes. When there is obstruction to fusion, or when fusion becomes difficult, a deviation of one eye may take place. If this process occurs before the age of 16 the eye will usually deviate in; if after, it will usually deviate out.

The most common obstructions to fusion are muscle pareses and marked differences in refraction between the two eyes. Eyes which are injured, with resultant poor vision, commonly tend to deviate. These usually turn out. All squints, then, are binocular. That is, one eye fixes and the other deviates. Many individuals alternate their deviation, having the ability to fix with either eye, but not with both simultaneously.

The parents will commonly notice that the squint has occurred after some illness. Usually, in these cases, a marked difference in refraction between the two eyes will be found. The child who heretofore has been able to reconcile these differences and maintain parallelism of the two eyes unconsciously gives up the fight to maintain parallelism (orthophoria) as the result of the illness.

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Presented before the staff of Childrens Hospital, New York City, October, 1945.

The deviation results from the unconscious attempt to throw the troublesome image (of the eye with the greater refractive error) far out of the field of consciousness.

Nervous children, or those with nervous disorders, may show a squint which is not primary and which disappears when the underlying cause is removed. Again, as in tuberculous meningitis, the squint may be the first sign of a neurological disorder.

Some illnesses and certain head injuries may be followed by a paresis of one or more of the extraocular muscles. Diphtheria and meningitis are common offenders. Recently, we saw a child with a marked sixth nerve paresis following meningococcus meningitis. After three months this cleared up almost entirely, except for a slight diplopia in the extreme right field.

#### CLASSIFICATION AND DEFINITION

All muscle imbalances may be classified as either paralytic or nonparalytic.

They tend to fall into one of two categories: (1) phorias, or tendencies to squint and (2) tropias, or obviously manifest deviations. The first group comprises those who squint only when tired, hungry, cranky. The second group always show their squint. In a sense both are different degrees of the same process.

Three other terms, or prefixes, must also be understood. *Eso* (*tropia* or *phoria*) means to cross in; the so-called "cock-eye." *Exo* (*phoria* or *tropia*) means to deviate out; the so-called "wall-eye." *Hyper* (*phoria* or *tropia*) indicates that one eye is higher than the other. This latter, or vertical anomaly, is of great importance, as we shall see later on in this paper.

##### Classification

A—Paralytic

B—Nonparalytic

1—Accommodative

2—Nonaccommodative

All horizontal (or lateral) muscle imbalances (the *eso* and *exo* groups) tend to fall into one of the following four groups on the basis of disturbance of function:

1. Convergence excess; overconvergence for near, manifesting itself as an *eso* for near vision only. The eyes are parallel in distant gaze.
2. Convergence insufficiency; inability properly to converge in near vision; the eyes show an *exo* for near, only.
3. Divergence excess; excess of divergence for distance and parallelism in near vision.
4. Divergence insufficiency; decreased ability to diverge for distance, so that there is an *eso* for distance.

As a rule, a mixture of two of these eventually results; i.e., convergence excess and divergence insufficiency, with the eyes becoming crossed in for both near and distance.

## PARALYTIC SQUINT

These cases are due to a complete paralysis or partial paresis of one or more of the recti or oblique muscles. Normally, the eyes are essentially parallel in all movements except that of convergence. In the paretic eye this parallelism of movement is disturbed, with a consequent diplopia in the field of action of the paralyzed muscle. This diplopia may carry over into the other fields. It is not seen in the child who is born with paresis.

The eye muscles tend to be yoked together (paired) in the performance of specific functions. For example, the right superior rectus and the left inferior oblique are "yoke" muscles in the performance of "eyes up and right."



Fig. 1.—A left hypertropia. Note that the right eye is barely elevated in the "eyes up and right" position, whereas the left eye is half buried under the brow. This is due to a paresis of the right superior rectus muscle with a "secondary deviation" or overaction of the left inferior oblique muscle.

The following will serve to illustrate the manner in which a paralysis may disturb the normal movements of the eyes (as well as their normal positions) and thus lead to ocular difficulty. If we ask the patient to look up and right, the right superior rectus and left inferior oblique act together to perform this movement. Hering's law states that an equal impulse is given to each of the functioning muscles. Let us assume that it requires a fictitious charge of 10 to move each eye up the required amount, normally. Now, if the right superior rectus is paretic and an object is presented to the left eye (the fixing or dominant eye in this case) in such a manner that the eyes must look up and right, the left will move up normally and the right partially or not at all, dependent upon the amount of paresis present.

If the right eye is now made the fixing eye, and the object presented to it, the right superior rectus will make every effort at its command to move up; and thus may exert a stimulus of say 100. This same 100 (or in this case, 10 times the required amount) will also be given to the left inferior oblique, which will now carry the left eye far up and right (Fig. 1) so that it may even be buried behind the nose. This marked overaction is referred to as the "secondary deviation" of the normal or nonparetic eye, which occurs only when the paretic eye is the fixing eye. It is an important sign in determining the existence of paresis, as it causes a marked and obvious disturbance of parallelism.

The inferior oblique, in this case, through its constant overaction, becomes a powerful muscle. Changes then tend to take place in its antagonist (the superior oblique) which now has a much stronger muscle to work against. By the same token, the right inferior rectus having a weak superior rectus to work against, also becomes stronger. Similar changes tend to take place in the other muscles; so that what started out to be a right superior rectus palsy may end by becoming an esotropia (or exotropia). The vertical anomaly is still present, but it is masked by the lateral anomaly. It is estimated that well over one-half of the lateral squints are wholly or in part due to a pre-existing vertical muscle paresis. In these cases, any treatment directed toward the lateral muscles, alone, is doomed to failure in advance.



Fig. 2.—An esotropia. The left eye is turned in. The position of the light reflexes here serves to illustrate the Hirschberg test. Note that in the right eye the light reflex is in the pupillary zone just nasal to the center of the pupil. The corresponding image in the left eye is on the cornea over the iris border.

#### NONPARALYTIC SQUINT

The cases in this group are due either to some defect of accommodation or of vergence function (the convergence and divergence excesses and insufficiencies) or of both.

The accommodative group can best be explained by illustration. The normal or emmetropic eye (which has no refractive error) does not accommodate for distance, accommodates 1 diopter for 1 meter, 2 for .5 meter, etc. If a child has 5 diopters of hyperopia (farsightedness) he accommodates 5 diopters for distance vision; which means that he starts with an accommodational handicap of 5. If he is now called upon to read a book at 13 inches he must accommodate 3 diopters for that distance, plus the 5 he is already using for a total of 8. As accommodation and convergence go hand in hand, he overconverges by 5, and as a result the eyes may swing in and cross for near vision. As he goes through life he will also eventually tend to cross for distance as well.

If he is a myope (nearsighted) of say 5 diopters, he cannot see in the distance clearly without glasses. An object at 13 inches, which normally requires 3 diopters of accommodation and convergence, falls into his scope of clearest vision, without calling upon the use of his accommodation, which is relaxed. With this relaxation of accommodation, there may be an associated relaxation of convergence; as a result the eyes may swing out.

Where the squint is entirely on an accommodative basis the proper refractive correction will correct the strabismus. If the squint is partially on this basis the correction will clear up that part of it.

The nonaccommodative group is on the basis of some dysfunction of either convergence or divergence, with no associated paresis. This group has already been referred to in the classification.

The term, *amblyopia ex anopsia*, applies to the nonaccommodative group. It refers to the cases where a marked difference in refractive errors is found, between the two eyes. For example, the right eye may require no lens and the left a +5 with a cylinder. As a result of the difference in size of the two images presented to the brain, the child may unconsciously give up using the left eye, with the result that it swings in or out. When his vision is taken, the right will be normal and the left poor. In this type of case, if seen early enough, occlusion of the right eye, plus proper correction of the left eye will correct the squint and restore useful vision to the left eye. These children may get along well until some illness intervenes; with lowered "resistance" they give up attempting to harmonize the images from eyes of dissimilar refractive errors and squint supervenes.



Fig 3—Exotropia of small degree. Note that the right eye is fixing, whereas the light reflex in the pupil of the left eye is more nasally situated because the left eye is deviated out, causing the image to be displaced in. In this patient the visual axis is more centrally placed than is normally the case, so that the normal right eye has its light reflex centrally placed.

#### DIAGNOSIS

The pediatrician is obviously not equipped to go into an extended diagnosis of most cases of strabismus. He can, however, usually determine that the child has some imbalance. Often, this is grossly visible or the mother has noted that the child squints when tired.

There are, at least, three methods by the use of which the pediatrician can rapidly note an imbalance without the necessity of making an accurate diagnosis:

1. By having the child follow some moving object (such as a toy or light) in all the fields of gaze and by noting whether the eyes are or are not parallel. A secondary deviation may be easily noted in this manner. In doing this test, it is well to examine separately up and right, straight out to the right, down

and right, and similarly on the left, rather than to swing the object rapidly in a circle, without carefully noting the position of the eyes in each separate field.

2. Hirschberg test (Figs. 2, 3). When an individual fixes on a light (as a flashlight or ophthalmoscope bulb) an image of the light will be seen in the same place in each of his pupils. Usually, this will be seen just to the nasal side of the center of the pupil, as the visual line passes nasally to the center of the pupil. If a tropia is present, the images will not be similarly located in each eye. If the left eye is turned in, the image will be seen just nasal to the center of the right pupil and far temporally to its normal position in the left eye (Fig. 2). If the left eye is turned out, the image will be far nasal to its normal position (Fig. 3). It is not uncommon to find the image (in the deviating eye) completely outside the area of the pupil, over the iris or on the sclera. This is a very good test in infants who, while uncooperative, will usually look at a light long enough for these images to be rapidly noted.

3. Screen test. If a card (the size of a calling card) is slowly passed back and forth before the eyes, as the child is fixing on a light or other object, and an appreciable movement of the eyes occurs as the card is passed from one eye to the other, it is probable that some deviation is present. This test should be done at 13 inches and for distance (20 feet or more). Whether it is of sufficient amount to require care depends upon the extent of the movement noted and upon the symptoms produced by it.

Frequently, a child with a vertical muscle imbalance will acquire a head tilt. Hence, in all head tilts, the ocular muscle imbalances should be ruled out before making a diagnosis of torticollis.

#### TREATMENT

There are three cardinal rules which must be observed in the institution of treatment. (1) If there are no symptoms, no treatment is necessary. This is especially true of the phorias, which can frequently occur to a considerable degree without causing any complaint. (2) Treatment must be instituted as early as possible. This will prevent the strabismus from becoming worse, as a result of muscle contractures. It may save a potentially useful eye, as in the cases of amblyopia from disuse. Early treatment saves the child from acquiring a "cock-eye" complex. It is frequently one's experience that the parents dislike having the child miss school and hence will give much more cooperation during the pre-school ages. By the same token, the child dislikes wearing an occluder while in school.

The third rule is that treatment must, as far as possible, be on a rational basis; that is, it must be predicated on a correct diagnosis. In too many quarters it is still felt that the squint surgeon's entire armamentarium consists in a recession of one lateral muscle or a resection of the other. Since, as I have already pointed out, over one-half of the cases coming to surgery have a marked deviation of one or more vertical muscles, the operative approach must be directed toward the responsible muscles. There is no place in medicine for hit or miss surgery. It must also be pointed out that the parents must understand



that one operation may be insufficient. It is better to undercorrect and to operate again, than to render a cross-eyed child wall-eyed, or vice versa.

The first step in the treatment, then, is the making of as complete a diagnosis as possible, a procedure not always possible in the infant.

The second step is a proper refraction under a cycloplegic, preferably atropine. If glasses are prescribed, they should be given a fair test of about three months; and if after that period, plus proper supplementary orthoptic exercises (if deemed necessary) the squint has not been corrected, the case should be re-evaluated with a view to surgery. It is useless for a child to wear glasses for years in the vain hope that they may eventually help. An integral part of the refraction is the occlusion of the good eye where an amblyopic eye is present. This may restore the vision of the latter so rapidly as to be almost unbelievable. It is important to be certain that the eye is actually amblyopic and not blind due to the presence of some lesion.

In the case of a recent paresis, it is advisable to wait from several months to a year, in order to give the paresis time to clear up spontaneously.

#### CONCLUSION

An attempt has been made to give the pediatrician some insight into the complex problem of squint, without going into too great detail on this very intricate subject.

# HEART DISEASE IN CHILDREN IN A RURAL IOWA COUNTY— PARTICULARLY IN RELATION TO RHEUMATIC FEVER

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**R**HEUMATIC fever is one of the most serious and fatal diseases of childhood. Practically no data are available regarding the incidence of this disease in rural areas. The following report deals with a study undertaken to determine the incidence of rheumatic fever in a rural county in Iowa.

For a better understanding of the study of the incidence of rheumatic fever in Washington County, a brief review of some pertinent facts about this community is in order. The population of the county (1940 census) is 20,055. The largest town in the survey area is Washington, which has a population of 5,227. The county consists of farming and nonfarming areas. Most families live in one-family dwellings. The school population (children 5 to 19 years of age inclusive) is 5,058. The study was undertaken in cooperation with the Washington County Medical Society and the Washington County Public Health Unit. The Washington County Health Unit was set up at the request of the county medical society, and the two organizations function in close cooperation. The health unit consists of a full-time medical director, a supervising public health nurse, and two or three assisting public health nurses. The town of Washington has a full-time school nurse. The county medical society and the medical director of the health unit were extremely interested in the rheumatic fever problem and were anxious to undertake a survey in conjunction with the Iowa State Services for Crippled Children.

The school survey was carried out during the autumn of 1940. A physical examination of the heart was done for each school child by Dr. D. C. Barrett (local public health physician) under the supervision of the pediatrician, or the examination was made by the pediatrician himself. The older children were asked to find out from their parents if they had ever had rheumatic fever or chorea. The younger children were asked to have their parents fill in a questionnaire. Any child with definite or questionable heart findings or history was examined at a special clinic where complete information was obtained. The survey uncovered the following number of children with definite rheumatic fever and rheumatic heart disease, residing in the area:

- 11 rheumatic heart disease
- 3 rheumatic arthritis with questionable carditis
- 1 rheumatic arthritis without carditis
- 1 chorea without carditis

There were also six children with possible heart disease and one child with possible rheumatic fever.

We were aware that the school survey method did not reveal all children with rheumatic fever living in this area. There might well have been some in-

stances of mild rheumatic fever which were not recognized as such at the time of the attack and which did not leave any residual damage to be recognized at the time of the school survey. It is also known from the mortality statistics of the State Department of Public Health that four school-age children of Washington County died during the years 1937 to 1940 from acute and chronic rheumatic diseases of the heart.

It was decided that more reliable and complete information on the incidence of rheumatic fever could be obtained as a by-product of several well-planned, diagnostic, and follow-up, cardiac clinics held in this area over a period of years with the cooperation of the local doctors, nurses, and school officials. Through such clinics, held at three-month intervals, we have endeavored to check every child with onset of rheumatic fever from 1940 to 1945. It is believed that this method, with community cooperation, revealed practically all of the children with rheumatic fever. The school nurse and the public health nurses checked the absenteeism of the school children and whenever a child was found to have symptoms or signs suggestive of rheumatic fever, the parents were advised to have the child seen by their physician. The family physician or the nurse reported all children with definite or suspicious findings to the public health service for further study and referral to the diagnostic clinics.

The following is a tabulation by year of onset, of the number of children experiencing an initial attack of rheumatic fever:

Year of onset	Number of school children
1940	5
1941	1
1942	4
1943	0
1944	7
1945	3
Six-year period	20

There were also six children examined who had possible rheumatic fever during this period. The average number of children per year experiencing an initial attack of rheumatic fever in this rural area of Iowa is 3.3.

The incidence of the disease in the school population for a given year for this rural county was obtained. The accumulated records of our clinics were reviewed and the incidence computed for the school population as of 1945. It was found that twenty-seven school-age children residing in this county had either rheumatic heart disease or histories of rheumatic fever without definite carditis. The mortality statistics of the State Department of Public Health (available for rheumatic fever since 1937) show four children of this school population who died from causes related to the rheumatic syndrome. Thirty-one children with rheumatic fever in a population of 5,058 give an incidence of 0.61 per cent.

All of the rheumatic subjects have been seen periodically at the cardiac clinics where diagnostic and follow-up examinations have been done. Some of the rheumatic subjects have become over age or have moved from the county. All of the subjects were living in 1945, and of the twenty-seven school-age children still residing in the county, fourteen had evidence of residual heart damage.

In reviewing the accumulated records of our clinics we also found that there were ten children of school age with congenital heart disease in this county (as of 1945). The mortality statistics of the State Department of Public Health (available for congenital heart disease since 1937) show deaths of four infants who would have been in this school population. Four additional children were found to have evidence of toxic myocarditis between 1940 and 1945.

#### DISCUSSION

Relative to some published incidence rates for rheumatic fever and rheumatic heart disease for areas differing in density of population and in climate, the Washington County incidence rate for school children is low. Paul<sup>1</sup> (1941), making a study of the incidence of rheumatic heart disease in the state of Connecticut, sampled the school population by examining all seventh-grade pupils in several industrial cities, semi-industrial cities, and rural towns. He reports the incidence of rheumatic heart disease for the industrial and semi-industrial cities and the rural towns as 4.1, 2.4, and 1.3 per cent, respectively. Sampson and associates<sup>2</sup> reported the incidence of rheumatic fever in school children living in Redland, California (selected because of its warm dry climate) as 0.57 per cent. The average incidence for the three California communities in this survey was 1.9 per cent. The incidence of 0.61 per cent for rheumatic fever in Washington County should be taken as a conservative estimate of the prevalence of the disease. Only subjects who had definite rheumatic fever or definite rheumatic heart disease were counted as belonging to the rheumatic group. We believe that since 1940 practically every child with rheumatic fever has been uncovered, but prior to this time a few of the school population could have had either rheumatic fever not recognized at the time or a questionable history which did not meet our criteria for inclusion in the rheumatic fever group.

Cahan<sup>3</sup> (1937) found the incidence of organic heart disease in the school population of Philadelphia to be 0.6 per cent. Rauh<sup>4</sup> (1936 to 1938) reports the incidence of organic heart disease in the Cincinnati school population to be 0.53 per cent. Of those with organic heart disease, 55 per cent had acquired lesions and 45 per cent congenital lesions. As of 1945 in Washington County there were fourteen school children with residual rheumatic heart disease and ten with congenital heart disease. For this county the incidence of organic heart disease for school children is 0.47 per cent. Of those with organic heart disease, 58 per cent have rheumatic heart disease and 42 per cent have congenital heart disease.

#### SUMMARY

The incidence of rheumatic fever in the school population of a rural county in Iowa is 0.61 per cent. The average number of children experiencing their first attack of rheumatic fever during each of the six years from 1940 through 1945 is 3.3. The number varied for each year from none to seven children. The incidence of organic heart disease for school children in this rural population

is 0.47 per cent. Of those with organic heart disease, 58 per cent have rheumatic heart disease and 42 per cent have congenital heart disease.

The author wishes to express indebtedness to the Washington County Medical Society for their active cooperation in carrying out this study, to Doctor Ruth Church and the staff of the Washington County Health Unit for arranging the diagnostic and follow-up cardiac clinics, and also to Helen Garside Kelly, M.S. for helping in the preparation of this paper.

#### REFERENCES

1. Paul, J. R., and Deutsch, J. V.: Rheumatic fever in Connecticut. A general survey, Connecticut State Department of Health, 1941.
2. Sampson, J. J., Hohman, P. T., Halverson, W. L., and Shearer, M. C.: Rheumatic Fever Incidence in School Children in Three Climatically Different California Communities, *Am. Heart J.* 29: 178, 1945.
3. Cahan, J. M.: Rheumatic Heart Disease in Philadelphia School Children, *Ann. Int. Med.* 10: 1752, 1937.
4. Rauh, L. W.: The Incidence of Organic Heart Disease in School Children, *Am. Heart J.* 18: 705, 1939.

## Special Article

### THE PEDIATRIC INTERN

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**D**URING the years of pediatric residency, the young physician formulates his approach to patients and their families. This paper discusses some of the problems confronting the intern in the hope that colleagues may find it helpful in orienting themselves.

More and more the pediatrician is called upon to focus his attention upon the parents as well as upon the child. This change in emphasis is making the pediatrician more aware of his role in the lives of parents and children. The pediatrician may well consider it a challenge to help all these people experience maximum mutual enjoyment.

#### THE NURSERY

The role of the pediatric intern on the newborn service is one which is only gradually attaining its deserved importance. One pediatric center has established the practice of having a full-time pediatric nursery intern who, in addition to his duties in the nursery, makes one or more home visits following the discharge of patients from the hospital.<sup>1</sup> In this way he is able to be of service to both mother and child in the postnatal period when trips to the pediatric clinic, superimposed on the mother's added responsibilities as well as on her physiologic weaknesses, would constitute a severe strain. Fully as important, however, is the fact that the intern, who otherwise sees patients almost exclusively in a hospital environment, gains the experience of observing the mother and infant in the home situation.

Firsthand knowledge of the home setting is a distinct asset, for without it the pediatric intern often experiences difficulty in recognizing all factors which influence the mother's attitudes during the neonatal period. He cannot be expected to know the mother's detailed life history. However, he must recognize that inadequate fulfillment of the parent's own emotional needs, sometimes going back to episodes in her own childhood, plays a role in the formation of attitudes at this trying moment. Only when aware of this can the intern adequately approach the clinical problems of the neonatal period.

Remarkable therapeutic value accrues from the investment of a few minutes daily at the mother's bedside during the post-partum period, when mother and baby are lying side by side. The mother notices the size of the baby, color of the skin, frequency or pitch of the cry, and color of the stools. Many questions arise. At this moment minor items loom large in the mother's mind. The common

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[Dr. Wessel wrote the manuscript while serving as an intern at the hospital.—Editor.]

procedure of relegating such discussions to the nurse does not mean that the intern should be unaware of them. This visit with mother and infant together, besides aiding the mother with her questions, also gives insight into the initial attitude of parent toward infant.

The intern must be aware of the many varieties of stimulus affecting the parent's attitudes. He is in a unique position to observe her initial feelings toward the new baby. An understanding intern may foresee, and possibly forestall, a feeding problem at 18 months.

One cannot overestimate the weight which mothers will place upon every remark the pediatric intern makes at this time. In many cases such casual remarks as "What a skinny baby," or "Such a big stomach," or "Such a big head," may be interpreted by the mother as indication of pathologic conditions, while in reality nothing was further from the intern's mind.

Similarly, the over-exuberant advocate of breast feeding, who outlines persuasively many of the well-known reasons for breast feeding, may be so convincing in his argument that, should there be an insufficiency of milk or some other contraindication to nursing, the mother may be certain that her infant will develop into a "weakling," may "lack immunity," or may turn out to be an "insecure infant."

Whatever positive factors there may be in favor of breast feeding, it should be clearly emphasized that a mother's unwillingness to nurse her infant must be given careful consideration before the intern uses persuasive urging. One must try to understand the factors responsible for this attitude. In many cases it is well to give up the attempt, rather than to have an unwilling mother nurse her baby "just because the doctor insisted." The majority of such situations lead to bottle feeding within a few weeks anyway, and quite frequently the early nursing experience is unsatisfactory to both mother and infant.

Thinking in pediatric circles concerning feeding habits is being considerably revised. The carefully detailed studies of Gesell and Ilg,<sup>2</sup> the clinical approach of Dr. Grover F. Powers and his staff in New Haven, and the popular writings of Dr. and Mrs. Aldrich<sup>3, 4</sup> have done much to create a more flexible attitude upon the part of pediatricians. These workers conclude that our former rigid attitudes may have been a little hasty; that babies themselves are capable of selecting a reasonable caloric intake if allowed relative self-determination. Many now consider the following to reflect a sound attitude: "Many children get along all right without clocks or scales. If your baby awakes five or ten minutes early, go ahead and feed him, and if he sleeps over time he can wait twenty or thirty minutes. You rest in the meantime. And don't worry too much over a few teaspoonfuls more or less. Most babies are pretty good judges of how much food they need."

This point deserves considerable stress. Regardless of what one considers the ideal, whether it be rigidity or flexibility of the feeding schedule, one must realize that the mother, regardless of anyone's advice, may be flexible in her own approach. A mother recently said, "Doctor, I haven't stuck to the schedule, and my baby's getting along all right. He's gaining weight, he seems happy,

and doesn't cry. But I expected you to scold me." Such an attitude on the part of the mother may well lead to a break in rapport between parent and intern, and proportionally limit his influence.

What to tell the parents of babies who appear to be somewhat retarded at birth is difficult. As is well known, there are many babies who are sluggish at birth and who continue to be sluggish for several months. The vast majority of these infants develop into normal children. Some are in the class of Mongolian idiots, others have spastic paralysis or cerebral palsy or a like condition. One's approach to the parents may be somewhat in this manner: "How does your baby look to you?" And quite frequently the mother says, "He seems a little sleepy." If this response is not forthcoming, it is wise for the intern to mention the fact in a gentle manner, and then proceed: "Your baby had a pretty tough time of it." (Or if it were an easy delivery, "Your baby does seem a bit sleepy.") Then he adds, "I think that we had better keep a pretty close watch over him for the next few months. We see many babies who seem sleepy at birth, and the vast majority develop perfectly all right. I think that your baby will be all right, but occasionally we find one baby who doesn't do so well. Therefore we want to keep an eye on your baby, and then we'll both feel better."

By the time the infant is 6 months of age, the well-trained pediatric intern can usually be more secure in his opinion. He can evaluate the developmental status, especially with the aid of Gesell standards. He can decide whether there is need of further psychometric examination. If handled properly, further examinations can give the mother the feeling that everything is being done for her infant. This may aid, rather than hinder, the mother's acceptance of the final decision. When a final conclusion has been reached, the clinical impression should be conveyed to the parents with gentle frankness and with care to give only such encouragement as is warranted.

Parents of retarded infants or of infants with congenital anomalies often have a sense of guilt. This may be latent, but occasionally it is freely expressed. The mother may feel that the infant's abnormality is related to something which occurred in her past life, either before or during pregnancy. A mother recently observed was certain that her infant had a serious congenital anomaly of the esophagus because she had gone to a night club during pregnancy.

#### FOLLOW-UP CLINIC

The six-week follow-up clinic gives the intern the opportunity to observe the mother, as well as the baby. Quite frequently it is the last hospital contact with the mother and infant, unless serious illness intervenes, and the remainder of well-baby activities are carried on by city health stations, or visiting nurse clinics. This is most unfortunate, since the intern loses sight of the developmental sequence of normal babies.

It is advantageous for the same intern who took care of the infant in the nursery and who saw the mother upon discharge from the hospital to see them again at the six-week period. Not only does this give the mother a sense of continuity, but also the intern can evaluate the adequacy of his earlier advice. Only in this manner can he improve his presentation and learn which points



need more emphasis. The questions which the mother poses may seem trivial to the intern, but they are important to her, and it is desirable that she have reassurance at this time.

#### THE OUTPATIENT CLINIC .

*The Parent.*—The problems facing the intern in the clinic are multiple. A child is admitted to the ward with a definite disease, or at least with complaints sufficient to warrant further investigation. However, the child is brought to the clinic because the parents think that he is not well. It is the function of the clinic, not only to evaluate the health status of the child, but also to understand the curious assortment of stimuli which prompt the visit. Such factors as illness of a sibling or of a neighbor's child, periodic school health examinations, poor eating habits, and many other daily events are frequent motivations for a clinic visit, although ostensibly the stimulus is "underweight" or "poor growth." Adequate care of the child involves more than a clinical examination. The parent's motivation for the visit must be understood and discussed to his or her satisfaction.

Children referred from school because of "heart murmurs" form a group that merits serious attention. Frequently the parents have been alarmed by the note from the school, when it was intended only that the child should have a careful examination to substantiate the opinion that the murmur was functional. For those cases that are clearly functional, a few comments along this line are sufficient: "Many children have murmurs when they are born, and some keep on having them throughout life. These murmurs do not mean heart disease and there is no reason why your child cannot do everything that any child does." On the other hand, if the murmur is a suspicious one, and further study is indicated, one might say, "It does sound a little suspicious, and I think to be on the safe side we ought to have an electrocardiogram and some other tests done. Then we'll know for certain."

The question of tonsillectomy keeps recurring in a pediatric clinic. Children are frequently sent in, either by an outside physician or by school authorities, with a recommendation for tonsillectomy. In many clinics the prevailing attitude is conservative and not in concurrence with the outside recommendation. Many say, "There is no need of those tonsils coming out," and with that the interview is ended. One can go a little farther in the discussion and say, "There is considerable disagreement among physicians as to when tonsils should, and should not, come out. We are primarily interested in children here; this is a children's clinic and we do not think it wise to make a child go through an operation unless it is absolutely necessary, and unless we can be certain of improvement in the child's health. After watching children over a period of years, we have concluded that unless the tonsils are actually diseased, and not merely large, the children are better off with them in until they are somewhat older. Then if they still bother, an operation may be necessary."

Many children are brought to a clinic with the complaint that "Johnny won't eat," or "He's always fidgeting." In the majority of these cases the intern can be certain that all is organically normal. But the job has just begun.

The problem must be worked through with the parent. Basic insecurity in the mother may make her expect too much of the child and create the feeding problem which is the main complaint. The intern must realize that there is no such thing as a mother per se, or a child per se. There is a complex family situation with social, economic, emotional, and cultural factors creating the background in which the child grows up. All of these factors affect the mother and child. The intern single-handed cannot be expected to solve the emotional problems of the mother, nor even get to the bottom of them, but he can recognize their importance in the life of the child. The help of a medical social worker is invaluable in assisting the intern to understand and deal with the situation. With more difficult problems the intern may seek the aid of the child psychiatrist. He may deal with the problem himself after consultation, or the psychiatrist may take over active treatment, but the intern must remember that when the psychiatrist steps into the picture, the pediatric intern does not step out. He remains the child's physician, and must fit into the over-all picture. He must also understand where the others fit in. At one pediatric center it is customary for the psychiatrist and pediatric intern to see cases alternately, and hence both are working continually with the family. In this manner, the child receives coordinated care; and the intern, with his contact with the family and with the psychiatrist, has a unique opportunity for training.

*The Child.*—It is axiomatic that the intern who chooses to work in a pediatric center must have an inherent liking for children. This entails respect and understanding of the child as a person. Within the last decade there has been increased discussion of the adolescent and his difficulties in asserting his own initiative amidst the cultural patterns of society, such as the restrictions of school, community, and family. The individual personality problems of the younger child, on the other hand, have been somewhat neglected in pediatric circles. This hiatus has recently been emphasized by Aldrich,<sup>5</sup> who feels that we begin to think of personalities too late in the child's life. Workers in the fields of child development and psychology have continued to gather pertinent information. A new concept of the fundamental needs of the child is coming to the fore, and it includes much more than calories and vitamins.<sup>6</sup>

The intern must be familiar with such needs as family security and opportunity for self-expression. He has to recognize their significance in the child's development, and the effect upon the child of their inadequate fulfillment. The child, no less than the adult, needs sympathetic reassurance to help him face life's situations. For example, the problems associated with "growth spurts," as characterized by the hyperactivity of the 2½-year-old child and described by Gesell and Ilg<sup>7</sup> as full of "thrustations and frustrations," appear different when considered in the light of personality development. It is during such a growth spurt that "good eaters" may become "feeding problems," and children who have been well "toilet trained" may slip back into "infantile habits." One who is familiar with the norms of personality development can recognize the forces at work and can interpret to the parents the relationship to the growth processes. Considerable tact and understanding are necessary, and the

intern must remain aware that both the child and the parent need constant reassurance.

The child who is old enough to express himself should be recognized as an individual when he comes to the clinic. If possible, he should be greeted by name, and if this is not possible, a common nickname, such as "Butch," is often acceptable. After this is done consistently, for a few visits, the child will sense "He's *my* doctor." The intern who succeeds in establishing this sort of relationship with the child has already won his confidence. With the older children, it is important to get them to express their own complaints. This often leads to a clearer concept of the clinical picture. It also gives the child the feeling that the doctor is interested in *him*, and not only in what his mother has to say.

Frequently the major portion of the physical examination can be carried on while conversing with the child. It is best to leave the examination of the ears and throat to the very end. Then tell the child what to expect and perform the examination quickly and deftly. It is helpful to ask the child, "May I look at your throat?" The child will frequently answer in the affirmative, and the procedure is simplified.

When the child is ill, recommendations should be conveyed to him. Even at 3 years of age a child can be told in simple terms: "Johnny, your throat looks a little red, and I know it hurts. It seems to me that if you stay in bed for a few days, and drink lots of water and milk and orange juice, you will soon feel much better." Often advice given in this manner is more completely carried out than when it is given only to the parents. When hospitalization is necessary, one may say, "Johnny, you don't feel well, do you? I think that if you stayed for a few days—maybe a week—upstairs with lots of other children, we could help you get well quicker. Your mother can come to visit you. As soon as you are better, we'll send you right home."

Rarely a child will agree to this procedure without qualms. The important point is that it has been discussed with him. It has not been decided upon by two adults, and then told as a complete surprise to the child. He has been forewarned. In many cases the child will bite his lip, try to smile, and agree. Never tell a child that he is "to stay just overnight," when that is unlikely. It is much better to emphasize the truth, "a few days or a week maybe," than to bring in a falsehood on a pseudotherapeutic basis.

Let us consider the child who has been referred from school because of a "heart murmur." It is not sufficient for the intern to satisfy himself and the parent that all is well; the patient also must be satisfied. The child, having been sent home from school with a slip requesting further examination regarding a "heart murmur," may have been placed on limited activity by the parents. This limitation, plus parental conversations regarding "Johnny's heart" and the conversations of the other children, may have culminated in an over-consciousness of the "heart condition." Once this idea becomes fixed, it may play an important role throughout the rest of the child's life. If the intern is certain that there is no cardiac disease, let him approach the child: "Johnny, there is a little murmur, a little unusual sound there; it is the kind of sound we often

hear in children's hearts. It doesn't mean that anything is wrong. You can run around and play football and go roller skating just like other children." On the other hand, if the clinical picture warrants study, the child may be told: "I don't think that there is anything wrong with your heart, but I think we ought to make some tests so as to be certain. When we get them all done, you come back and see me and we'll talk about it."

Negative tests mean that the child can be told that all is well. If the tests show evidence of active rheumatic fever, explanation to both the parent and the child is indicated. One may say, "Johnny, the tests show that there is a little infection going on, and I am afraid that you are going to have to stay in bed for a few weeks, or maybe even longer, and then you'll feel better. If you don't stay in bed and rest up now, you'll be sicker, and then we'll be sorry." A valuable addition to this regimen is to interest the child in reading and drawing. Requesting that he bring back pictures on return visits often stimulates sedentary activities.

The child with a chronic cardiac condition necessitating limited activity presents a difficult problem. Most of these children are well enough to be up and around and to attend school, although not able to participate in athletics. They readily become chronic invalids far beyond all justification. One can approach the need for limited activity by placing the responsibility directly upon the child. "Johnny, you know as well as I do that you were pretty sick a while back, and I think that you will have to be careful for awhile. Sit down and rest when you get tired; let's leave out baseball, football, and roller skating, and maybe in a few months when you get stronger you can do more." A direct conversation with the child makes it easier for the mother to maintain the necessary limitations of activity.

It helps to arrange clinic procedures so that skilled laboratory technicians or nurses do the vaccinating and other "needle work." Then the child will have no occasion to associate a painful experience with the intern. It is important to approach the child honestly. "This is going to hurt a little, but we are going to have to do it. You hold still and we'll be all done in just a few minutes." Never should any painful treatment be preceded by, "This isn't going to hurt at all," when it involves a painful jab with a 3-inch needle. After an explanation many children will cooperate willingly, and it is fascinating to hear a child exclaim, "You got it, didn't you?" even after the intern has had considerable trouble in carrying out the procedure. One can often obtain the cooperation of the youngster by asking at the beginning "Which arm do you prefer?" The child often chooses an arm, and then will forget all about his original fear. An uncooperative child is scarcely an indication for severe scolding and characterizing him as a "bad boy." It is better to sympathize with the child, and say, "That was pretty tough, wasn't it, Sonny? But it wasn't half as bad as you expected. I'm sorry that I had to hurt you, but it's all over now."

There are many other aspects of clinic activity which might be mentioned here. For example, when referring parents and children to another clinic, be honest; tell the child and mother, "I want the doctor who knows a lot about

bones (or skin) to see you." Care must be taken not to create an atmosphere of something being "terribly wrong" because the child is being sent to another clinic. It is better to convey the idea that the aim is to utilize all the available resources.

#### THE WARD

*The Parent.*—The intern on the ward, as the representative of the hospital staff, must, in addition to giving the required medical care to his patients, deal with their families. Too often his attitude is: "We'll take care of the baby; you go home and forget about the child. That's our business." The child is, of course, the parent's business, and the intern's function includes allaying parental anxieties as well as caring for the child. In many large institutions the first contact in the hospital is a somewhat hurried interview in the admitting room. This often occurs in the early hours of the morning. The admitting physician is usually harassed by lack of sleep; the mother equally harassed by her own exhaustion and anxiety. The nurse often whisks the child out of the parent's arms and the mother is told: "That's all. Visiting hours are Tuesday from 3 to 4." Such an introduction to hospitalization can only produce increasing concern on the part of mother and child alike.

Every effort should be made to allow the parents, before they leave the hospital, to see their child safely in bed, if only through a window. It is helpful to give the mother an opportunity to talk with both the intern and the nurse who will be in charge of the child. She can then be told the hospital's method of conveying information regarding patients. If the "call system" is in effect, the intern may suggest: "Phone me between 2 and 3 o'clock tomorrow afternoon. I'll be glad to talk with you about your child." The anxious parent is often relieved by a statement like this: "The nurses and doctors on this floor are not chosen any old way. They work with children because they like children, and because they have had special training for this purpose."

It is disturbing to the child to have the parents say "good night," and add, "Mother is going downstairs for a cup of coffee, and will be back in ten minutes," when this is untrue. A nurse or intern within hearing distance can usually control such attempts. Most children will accept the statement: "Mother is going home to take care of the house and the rest of the family, and she will be back in a day or so to see how you are. As soon as you are well we will send you back home." Even with such a statement many children cry and fuss. However, the child knows the truth, and is thus spared the additional injury of losing confidence in his parents and in the doctor.

At this point parents should be told something about the child's illness. It is well to avoid exaggerations or belittling of the illness. Parents should be told only what can clearly be deduced from the history and physical examination. One can frankly say, "By morning, when we have laboratory reports and x-rays available, we will be able to tell you more."

Parents should have the illness explained to them in clear, simple terms. Meningitis, representative of an acute severe illness in children, may be handled

thus: "I think that your child is pretty sick. You know that yourself, that's why you brought him here. When a child gets a sore throat or a cold, the germ sometimes goes throughout his body, and once in a while settles inside his head. Then we say the child has meningitis. I am not certain whether your child has this or not; but by doing a lumbar puncture, that is, by sticking a needle in his back, and taking out a little fluid, and studying it in the laboratory, we can tell whether or not he does have meningitis. There are several kinds of meningitis; some are very serious, and some are not. By tomorrow we will be able to know which one, if any, he has and to tell you about the success of our treatment with other children with the same illness." The family will appreciate being allowed to call back after the lumbar puncture. If there is evidence of meningitis, they should be told. If the examination is negative, there is additional reason to report and thus relieve anxiety.

Many will disagree with this approach. Such detail, they will say, is unwarranted. I believe it to be sound practice to acquaint parents with any traumatic experience the child may encounter. Then they have a basis for interpreting the child's descriptions of "those awful needles" or "those horrible enemas," and will be less afraid that their child is being experimented upon. A child's condition, which warrants a lumbar puncture, is surely the parents' business, and it is the intern's responsibility to keep them informed.

In the case of the moderately ill child, such as one with pneumonia, the intern might say, "Your child has a very severe cold, and the x-ray reveals a small area of pneumonia. Since we have had the new drugs, pneumonia isn't as serious as it used to be, and we find that the children usually get well in a week or ten days. We like to keep them in the hospital until the x-ray shows that the chest is clear again."

The intern caring for a fatally ill child, as one sick with leucemia, is confronted with many problems. He must wait until he is certain of the diagnosis. Out of sight and hearing of the child, he may then approach the parents: "You know, your little boy is quite sick, in fact very sick. That's why you brought him here. I am afraid that he is going to be sick for quite a while. I think that we can make him a little more comfortable with blood transfusions and some medicine. But I'm sorry to say that's about all that we can do for him."

The parents should also be told that the child does not know of his fatal illness, that he has been told that he is quite sick, and that he will be sick for some time. Urge them to make him as happy as possible and to withhold their tears when in the child's presence.

Many parents impulsively want to take the child at once to another hospital. It is vital that the intern readily agree to aid in this transfer and to offer to make connections for them elsewhere. After the initial discussion or at a later date, he can often add a word or two which will discourage "shopping around," if the problem is hopeless. But initially it is better to accede. Otherwise the parents are likely to mistrust the physician. If there are known pediatric centers where new treatments are being studied, the intern should tell them frankly, avoiding unwarranted encouragement.

*The Child.*—The intern is at the same time physician to the child and mediator between the hospital staff and the parents. These two functions must be kept clearly in mind.

The initial physical examination of the child should be performed carefully and slowly, with every effort to gain confidence. Arriving at a tentative diagnosis, it is wise to tell the child, in words suited to his age, something about his clinical status. "Your throat looks sort of red to me, and I know it is pretty sore. We'll give you some medicine for it, and I want you to get lots of sleep and drink lots of water and fruit juice, and when your temperature stays down for a day, and your throat is all better, you will be able to go back home"; or "You have a bad cold in your chest, and the picture that we took shows a little shadow, or pneumonia, as we call it. As soon as the shadow disappears and you feel all right you can go home. We'll give you some pills so that you will get well faster."

Good rapport should be sought on this initial contact with the child, for his cooperativeness during the entire hospitalization and even future hospitalizations is dependent upon it.

The performance of lumbar puncture is an event which may occur during the first hours of hospitalization. This may have serious emotional consequences. The procedure should be explained to the child: "Johnny, in order to find out exactly what is the matter with you, and in order to make you get well quickly, we have to stick a tiny needle in your back. It is going to hurt a little, and if you hold still we'll be all done in just a few minutes." Sedation and local anesthetic are helpful.

Answer the child's questions regarding when he will be able to go home. It is sufficient to say "As soon as the x-ray shows that your chest is all clear," or "As soon as you are stronger and feel better." The intern should be careful not to be led into saying "tomorrow" or "Monday," unless it is a certainty. It is important to give the child an answer, and better that it be true to the situation, than an untruth coined in an effort at appeasement.

The maintenance of adequate fluid intake is important on a pediatric ward. It is a common practice to tell children, "Drink a lot of water or else you'll have to have the needles." In this manner, the parenteral fluid is held up as a punishment, a technique open to serious question. It is better to handle the situation in this manner: "Johnny, you should drink about ten glasses of water today. Let's see if you can drink that much, and then we won't have to bother with any needles. Okay?" The distinction between these two methods may seem trivial. In the first case the frequent "needles" are punishment. In the second case the intern is someone who is trying to help the child escape certain painful experiences which are sometimes inherent in hospitalization.

The alert intern is sensitive to the adequate psychological adjustment of the children on his ward. A quiet, shy child, who after several days still does not make friends with the other children, or a child who is continually belligerent and a troublemaker, may be an unhappy child floundering in an intolerable home or school situation. He may need expert psychiatric care.

The chronically, fatally ill child, such as one with leucemia or Hodgkin's disease, is a constant problem. After a few weeks in the hospital these children gain considerable insight into their own status, and often ask, "When will I get well?" or "Will I ever get well?" and an occasional child will say, "I know that I am not going to get better." The handling of these children is a difficult problem and necessitates the greatest possible sensitivity and sympathetic understanding. It is *not* sufficient to adopt the attitude: "He's going to die anyway, so there is no need to worry about him." One can say, "Johnny, you've been sick for many weeks. You know that as well as I do. I'm afraid that you are going to be sick for a while longer, perhaps quite a while. You are going to need a lot of rest and sleep, and pretty soon you'll feel better. But you may feel a little worse for the next few days, and you just try to make the best of it. If you have any pain, you let me know, and I'll give you some medicine that will make you more comfortable. When you feel sleepy, just try to sleep."

Care is needed in such situations to avoid giving the child a feeling of hopelessness and of being alone in the world. The intern must constantly guard against this and see to it that such a patient gets plenty of nursing attention in order to give him that added security of having someone near him.

The intern who manages to have a stock of fairy tales, poems of the "Christopher Robin" variety, or who can display familiarity with "Dick Tracy," will find it much easier to develop good rapport. Even more than adults, children have the need of socialization and conversation. The intern who can succeed on this score will win the confidence of children.

It is impossible for the intern to be an expert in all of the fields mentioned, but the large institution provides colleagues oriented in the various points of view. He may learn much from the psychiatrist and the social worker about the child's personality and the various forces which aid or impede its development. Such insight will be of inestimable value in his own relationships with children and their families, and will also better prepare the pediatric intern for the role which he will eventually play in his community, that is, the person who "knows all about children."

In short, the aim of the pediatric intern is to increase the general well-being of the child, and to learn as much as he can from each individual child who comes under his care. He must utilize all the available resources in his institution for the advantage of the child and also for his own educational advancement. By "the child" we mean a dynamic, individualistic personality with all the problems of adjustment—to family, school, community, sickness, and hospital—which surround a growing individual in our society.

#### SUMMARY

Various aspects and implications of the relationships between the pediatric intern and the children under his care, and their families, have been discussed. Emphasis has been placed on the ever-important factor of recognizing the individual, as well as the disease. It is hoped that this orientation may aid medical



school graduates entering pediatric services to foresee the dimensions of their relationships with children and parents. It may aid them in attaining their own goal, that of giving to those under their supervision and guidance the best possible care at the earliest possible date.

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#### REFERENCES

1. Jackson, E. B.: *Am. J. Orthopsychiat.* 15: 89, 1945.
2. Gesell, A., and Ilg, F. L.: *Feeding Behavior of Infants. A Pediatric Approach to the Mental Hygiene of Early Life*, Philadelphia, 1937, J. B. Lippincott Company.
3. Aldrich, C. A., and Aldrich, Mary M.: *Babies Are Human Beings: An Interpretation of Growth*, New York, 1938, The Macmillan Company.
4. Aldrich, C. A., and Aldrich, Mary M.: *Feeding Our Old Fashioned Children; A Background for Modern Mealtimes*, New York, 1941, The Macmillan Company.
5. Aldrich, C. A.: *The Relation of Pediatric Preventive Medicine to Mental Hygiene, Psychosom. Med.* 7: 368, 1945.
6. Frank, L. K.: *The Fundamental Needs of the Child, Ment. Hyg.* 22: 358, 1938.
7. Gesell, A., Ilg, F. L., Learned, J., and Ames, L. B.: *The Infant and Child in the Culture of Today: The Guidance of Development in Home and Nursery School*, New York, 1943, Harper & Brothers.

# The Academy Study of Child Health Services

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## STATE REPORTS AND THE STUDY OF CHILD HEALTH SERVICES

One of the fundamental objectives of the Study of Child Health Services is to stimulate state, county, and local agencies to inquire into health conditions within their own areas in order that health services for children may be improved. The Academy is even now well along the road toward the attainment of this objective. The extent to which it has already been reached is demonstrated by an increasing appreciation of the importance of the reports of the Study to be prepared at the state level. During recent months as the Study has progressed and as we look forward to constructive use of the factual data, the emphasis has shifted from the national report to state reports. This significant development has arisen directly from the genuine interest and success of state chairmen, their executive secretaries, and study committees in organizing and conducting the Study in their own States. The Central Executive Staff has received repeated requests for detailed breakdowns of the statistical information suitable for a description of services and facilities for child health, not only for each State as a whole but also for the individual counties and communities within each State. The repeated question, "What information are we going to get out of the Study for our own use?" signifies that state chairmen and others who have been active in the Study are really concerned in seeing that their investments of time, effort, and money produce local as well as nation-wide results.

In response to these requests, the Executive Staff has agreed to return to the States an analysis of the information broken down to the level of counties and cities of 10,000 or more population. Despite the increased work involved, the Executive Staff has recognized the validity of the requests and has planned accordingly with a great expanded Central Office and statistical division. The addition of new staff members, described in the October issue of the JOURNAL, and the present search for adequate quarters are evidence of the intention to complete the Study in the shortest possible time.

As first announced in the August issue of the JOURNAL, three regional conferences were planned so that members of the Central Executive Staff might meet with state chairmen, executive secretaries and other state representatives for a free interchange of opinion; state representatives explaining what they wish to receive and the Central Staff describing the amount and type of material which can be made available. These meetings were held during September in Chicago, San Francisco, and Washington, D. C. From all points of view they were highly successful. All were well attended with representatives present at one or more of the three meetings from all but four States and the Territory of Hawaii. The officers of the Academy were represented by Dr. Durand at San Francisco, Dr. Hill at Washington, and Dr. Grulee at Chicago. Also a great deal of impetus was given to the Washington meeting by the presence of the Committee for the Study of Child Health Services.

Each of the meetings occupied two full days, opening with a general session at which the director of the Study described the purpose and plan of the meetings and introduced other members of the Executive Staff. Dr. Montgomery Blair, Jr., summarized the present status of the state programs and reviewed in general terms the progress of the Study to date. Mrs. Maryland Y. Pennell outlined the statistical procedures involved in editing, coding, and transcribing the data from the completed questionnaires to the punch cards, and the preparation of the tables from the punch cards. Dr. Charles L. Williams, Jr., discussed proposed methods of analyzing the material in relation to grouping of counties on the basis of their metropolitan character. This method of county classification has already

been described in some detail in the July issue of the JOURNAL (pages 117-120). The final discussion of the morning session was conducted by Dr. Katherine Bain who presented in broad terms the proposed outline for state reports.

The Executive Staff having outlined the work of the Central Office, the rest of the two day meeting was devoted to obtaining from state chairmen or their representatives reports of progress, problems, and specific recommendations concerning the type of material to be returned to the States. There were so many questions in the minds of the Central Staff as to just what the States want that, in order to cover all details, the meeting was broken into subcommittees to consider one or more sections of the proposed state report with the specific questions and tables related thereto. A state chairman was appointed to lead the discussion of each of the five groups with a member of the Executive Staff serving as secretary for each group. The entire morning of the second day was given over to these group discussions with a general session in the afternoon at which the findings of the five groups were presented by the chairmen for open discussion.

The assignments given the five groups covered the following topics: *Sub committee A* discussed that portion of the outline dealing with the summary section including the table forms showing volume of medical care for newborns, infants, and older children. The table forms considered by this group included those set up to answer such questions as: How does the volume of medical care vary with respect to the metropolitan and rural county groupings of the State; do differences exist in the volume of care rendered to white and nonwhite children; what is the general over all picture of health supervision for children; what are the differences in medical and dental care in metropolitan and nonmetropolitan areas of the State? *Sub committee B* considered information and table forms related to the distribution of physicians and dentists and the care rendered by specialists and general practitioners. Some of the questions to be answered by this section of the report included: Are physicians and dentists available in all areas of the State to care for children; are specialists as well as general practitioners available; how far do children have to travel to see a specialist, who actually takes care of the children, how many visits are made to children by general practitioners compared to the number made by pediatricians? *Sub committee C* reviewed the table forms concerning an analysis of the practice of general practitioners, pediatricians, and dentists with regard to such specific items as: What is the age, sex, race, and medical training of general practitioners who care for children, in relation to the total number of physicians; to what extent do general practitioners request pediatric consultations; are hospitals which admit children readily available to the general practitioner; what hospital facilities are readily available to the pediatrician; what is the age, sex, race, and training of dentists who care for children? *Sub committee D* considered information relating to hospital care for premature, newborn and other infants and older children. The table forms showing the analysis of this information were designed to answer such questions as: Where are the hospitals that admit children; what is the relation of their location to the centers of population where the children live, how many beds and bassinets do they have; what is the volume of care rendered to children by large and small hospitals; what are the variations in the type and volume of service in the metropolitan and nonmetropolitan areas, what is the location, volume of care, and character of service of the special hospitals such as tuberculosis, orthopedic, nervous and mental, contagious disease and other hospitals? This group also considered information on outpatient services, their location, volume of care rendered, and the availability of such services for pediatric specialties. *Sub committee E* discussed the tables dealing with health supervision of children rendered by official and voluntary community health services. The factors to be analyzed include: volume of supervision given; type of personnel responsible; and location or extent of services in relation to metropolitan and rural areas. Separate table forms were reviewed for well child conferences, dental services, mental hygiene services for children, services for physically handicapped children, communicable disease control, school health services, and public health nursing services.

These are only a few of the points which served as the basis of extensive discussions in these committee meetings. For the most part these discussions were limited to subject matter considered appropriate for state reports. There is a great deal of additional information available from the questionnaire which does not lend itself to a breakdown for each individual county. For example: in many counties there are too few pediatricians to provide sufficient information showing the characteristics of their private practice for that particular county, whereas in the national report the character of pediatric practice will be shown from the point of view of the age of children seen, the proportion of practice given to health supervision, the ratio of office, home and hospital visits, the frequency of consultations with general practitioners, the hours spent in public health activity, the extent of group practice and prepaid service, etc. Those data which are suitable for the national report but not for the state reports were described only in general and brief terms in order to complete the picture.

In the afternoon of the second day the committees reported their recommendations to the full meeting. Space does not permit a recording at the present time of all the recommendations and discussions. However, certain rather fundamental points were brought out which should be noted here.

A great deal of thought was given to the most satisfactory method of grouping counties in order to show health services available in densely populated areas where hospitals and medical centers are more apt to exist, in comparison with urban and remote sections of the country. As indicated above, this point has been described in an earlier issue of the JOURNAL and will not be repeated here except to state that a revised terminology is being used for the sake of clarity. Rather than classifying the counties as belonging to class I, II, III, IV, V, as was done heretofore, they will be given descriptive designations as greater metropolitan, lesser metropolitan, adjacent, semirural, and rural. Several of the state chairmen expressed the desire to receive the information tabulated not only in accordance with these county groupings but also for each individual county. Although this will involve considerably more work for the statistical staff it can be done for much of the data. A few of the state representatives suggested further modifications of the proposed method in accordance with trade areas in the different states. The final decision was that the Central Office will send to each state office a map showing classification of counties by the present method. These maps can then be used by the state chairman and others to determine the applicability of the method to each particular State. Suggestions for changes or regroupings of counties will then be submitted to the Central Office. A recommendation of considerable significance was that an attempt to break down the data for white and non-white patients was impractical, since so often the information was either not obtainable or not reliable. It was agreed that this differentiation could be made available for those States which can obtain reliable information and omit it for the others. It was also admitted with regret that it would probably be impossible to obtain reliable figures from item fourteen of schedule III-B which asks for the total number of patients seen by a pediatrician during the year.

The question of the confidential nature of certain portions of the information being obtained was again discussed. It was agreed that, when requested by the state chairmen, schedules of series I (Hospitals) and series II (Community Health Services) may be returned to state offices. However, special emphasis should be placed upon the confidential nature of the schedules of series III which deal with the private practice of physicians and dentists. The responsibility for maintaining the confidential nature of these schedules rests with the state offices until the schedules themselves are sent to the Central Office. The Central Office then assumes responsibility to keep them confidential, and will destroy them after the desired data have been transferred to punch cards. These punch cards will not include anything which might identify an individual, so that there will be no need of considering them confidential. Therefore duplicate punch cards may, if requested, be returned to States which desire to make further statistical analyses appropriate to local conditions.

Even after the free and detailed discussions of these two day sessions, it was very apparent that there were still many unanswered questions and uncertainties as to just how the tabulated material prepared in the Central Office is to be translated into a description of child health services at the state level. It is expected with a reasonable degree of assurance that answers to many of these questions will be found during the process of preparing a report for North Carolina, our pilot State. This report is now being written by the Executive Staff in collaboration with Dr. Arthur H. London, Jr., State Chairman and member of the Academy Committee for the Study of Child Health Services. Thus, North Carolina, which was used first as a pilot in the collection of the desired information, then in the analysis of the data, is again being used as a pilot in the preparation of a suitable report. By the time tabulated data are ready to be returned to other states, the North Carolina report should be in the hands of all state chairmen to serve as a sample for those who wish to use it as such.

The present time schedule calls for a preliminary report of the North Carolina Study to be presented at the meeting of the Academy in November at Pittsburgh. By the first of the year this should have been completed and in final form subject to revision by the North Carolina Pediatric Society. By spring the schedules from all States should be in the Central Office, and at the same time material for some of the States should be ready to return to them. By summer the analysis of data should have been completed for a sufficient number of states, so that a first draft of the national report could be started, aiming at the original objective of completing the report of the nationwide Study with all States included by the beginning of 1948.

JOHN P. HUBBARD

# The Social Aspects of Medicine

## THE PERMANENTE HEALTH PLAN

KATO VAN LEEUWEN, M.D.  
BERKELEY, CALIF.

The present Permanente Health Plan is an outgrowth of the medical care prepayment plan that was offered by the Henry Kaiser organization when it was engaged in huge construction projects in isolated areas.<sup>1</sup> Since no pre-existing medical and hospital facilities were available, these had to be provided to the many people employed. A similar problem was created after Pearl Harbor by the influx of warworkers to the areas where Kaiser was establishing shipbuilding plants. Sidney R. Garfield, M.D., who had been in charge of the medical care program during the construction of the Los Angeles Aqueduct in Southern California and the Grand Coulee Dam in Oregon, was asked to organize similar set-ups. As a result, the Northern Permanente Foundation was established to serve the employees of the shipyards in Vancouver (Washington); the Permanente Foundation Hospital in Oakland (California) and the Permanente Field Hospital in Richmond (California) for the workers of the Richmond Shipyards; and the Southern Permanente Hospital for the people employed at the steel mill in Fontana (California).

In the beginning only employees were taken care of on a prepayment plan. Dependents were able to secure medical care at the Permanente Foundation on a fee-for-service basis. Membership in the Health Plan was first opened to the immediate families of the employees at Northern Permanente in September, 1944, and at Permanente Oakland and Richmond in May, 1945. At present the Family Health Plan in the East Bay area is available to the public at large in groups or for individual membership. Quite a few employee organizations (as for example the United States Department of Agriculture, the University of California, the Key Route Transportation System) and labor unions have endorsed it.

The Vallejo Housing Projects situated twenty-five miles from Oakland and accommodating employees of the Mare Island Navy Yard contracted with the Permanente Foundation for medical care of the tenants. A Family Health Plan was organized and two outpatient clinics were established in 1945.

### MAJOR PRINCIPLES

The operation<sup>2, 3</sup> of the Permanente Foundations is based on prepayment (to distribute the cost of medical care over a longer period of time and among a greater number of people), group practice, and adequate facilities. The Permanente Health Plan differs from the usual health insurance in that the patient deals directly with the medical organization rather than through the medium of an insurance company.

### COST TO THE SUBSCRIBER AND COVERAGE

Health Plan members in Vancouver pay 80 cents a week for each adult member. Children, 16 years of age or over, are considered adult members. Fifty cents per week each is charged for the first, second, and third child under 16 years. Any other children under 16 years are covered without additional charge. Fees for membership are collected weekly by pay roll deduction from the employee-member. During vacation, illness, and temporary layoffs health protection may be retained if payment is continued.

All employees at the Kaiser Company Shipyard in Vancouver are eligible and are asked to sign up for the Health Plan when first enrolled in the shipyard. No physical examination is required for membership.

Subscribing members are entitled to physician's care up to one year's treatment for any nonindustrial injury or illness, its recurrences, and complications. Hospitalization and nursing care are given 111 days for any one illness and include food, medicines, x-rays, basal metabolism, electrocardiograms, use of surgeries and the laboratory. Private hospital room and private nurse are provided when ordered by the attending physician. Medical care for contagious diseases is included and the cost of hospitalization (at the County Hospital) is borne by the Northern Permanente Foundation. Pre-existing chronic illnesses are covered, provided the member has been on the plan for ninety days or more. A \$10 charge is made for tonsillectomies for children under the age of 16 years. A \$50 charge is made for maternity cases, that is, if the member has been on the plan for at least ninety days prior to delivery. This includes hospitalization and medical care before and after birth. Medicines and blood transfusions, medical and surgical supplies as used or prescribed by the attending physician are furnished, with the exception of vitamins, hormones, and permanent corrective appliances (including artificial limbs and eyes, and glasses). No dental care is given except for dental x-rays if prescribed by the attending physician for the treatment and diagnosis of systemic diseases. Ambulance service is available within a radius of thirty miles of the Foundation when deemed necessary by the doctor. Emergency service away from home is limited to \$250. The treatment of mental diseases and tuberculosis is not covered (State laws provide for this care).

The Oakland-Richmond Family Health Plan is less expensive and less inclusive than the Health Plan available in Vancouver, Washington. The costs of the former are 60 cents a week to the subscriber, 75 cents for the spouse, 30 cents for one child, and 60 cents for two or more children. Diagnostic and professional service is given for pre-existing conditions but a fee is charged for hospitalization, operating room, and medication. Hospitalization for contagious diseases is not included. A charge is made for medicines prescribed for outpatients. Services covered by the Health Plan are rendered only at the Permanente Foundation Hospitals and Clinics and must be by Permanente physicians.

A fee of \$2.00 is made for the first housecall by a doctor per illness. No charge is made for home visits by nurses.

All individual members who apply are subject to physical examination. This is not a requirement for group members.

An alternative plan has recently been offered. It is modeled after the Ross-Loos plan in Los Angeles. The subscriber pays 60 cents a week for himself and has full coverage as outlined in the Oakland plan, while the family is taken care of at reduced rates, namely \$1.00 per office visit and a reduction of 25 per cent on laboratory procedures and x-rays. A maximum of \$25 is charged for minor operations and a maximum of \$100 for major operations. Hospitalization is provided at regular rates. This plan was suggested to make the Health Plan more salable, because many people feel that \$8.45 a month for a family of four is more than they can afford.

#### ADMINISTRATION AND STAFF ORGANIZATION<sup>2, 4</sup>

The Permanente Foundations are charitable trusts governed by Boards of Trustees headed by members of the Kaiser family. Money to finance the original facilities was lent by Kaiser to the Permanente Foundations. They were set up in such a manner that there would not be any profit incurred by anyone in the Kaiser organization. Any funds that may be accumulated by the Foundations are supposed to be used for such purposes as medical research, provision for new facilities in areas in need of medical care, medical care for the poor, and teaching.

During the war the medical staff consisted of 75 doctors in the Oakland-Richmond area and 35 doctors in Vancouver. Fontana had 7 physicians on its staff. The amount of time spent at the hospital and outpatient departments by each doctor depends on the organization of each department and its case load.

Chief administrator of all Permanente Foundations is Sidney R. Garfield, M.D. Each hospital has a medical director appointed by him, assisted by a lay administrator.

Executive Committees consisting of the Medical Director, Chief of Staff, Heads of Departments, and elected staff officers were organized in Oakland and Vancouver by the doctors, in order to discuss policies relating to administrative and nonmedical aspects of the hospital, its personnel, and the medical care furnished. They serve in an advisory capacity only. The final decisions are made by the Chief Administrator.

There is an active staff association whose elected officers preside over regular meetings at which scientific papers are delivered and pathology conferences and clinical seminars are conducted. Business meetings of the staff association are held monthly.

There are additional committees in the Oakland hospital on Industrial Hygiene, Lay Education, Venereal Disease, Public Health, Research, and Pharmacy.

The Oakland and Vancouver hospitals have been approved for internship and mixed residencies by the Council of Medical Education and Hospitals of the American Medical Association and also for the Senior Cadet Nurse Program by the State Boards of Nurse Examiners. This not only helped to relieve the shortage of personnel but also proved to be a stimulus to the professional staff and of value in the maintenance of good quality medical care.

#### SALARIES OF PROFESSIONAL PERSONNEL

Most doctors are started on salaries of \$400 to \$600 a month. The heads of departments usually receive from \$700 to \$1,000 a month. A yearly increase of \$1,200 per annum was given to some of the doctors during the war. Registered nurses receive from \$180 to \$200. Supervisors receive up to \$225 a month.

#### FACILITIES

The Northern Permanente Foundation Hospital at Vancouver, Wash., is beautifully situated in a prune and pear orchard on a hill overlooking the shipyard and the Columbia River. It is a one-story building divided into three units. The inpatient departments are patterned in the form of Greek crosses at the centers of which are nurses' stations, drug, linen, service, and utility rooms. The operating rooms are arranged in a circle around a centralized work and sterilizing area; patients enter through exterior corridors, eliminating all cross traffic.

The hospital has a capacity of 335 beds (35 of which are for pediatrics) and averaged a daily census of 275 inpatients during the war. The outpatient department and first-aid station then handled about 1,000 to 1,500 patients a day (including approximately 75 pediatric patients).

Services include the following departments: surgery, orthopedics, obstetrics and gynecology, pediatrics, otolaryngology, ophthalmology, medicine including cardiology and endocrinology, allergy, dermatology and syphilology, urology, radiology, pathology, and clinical laboratory service.

The atmosphere is friendly. Waiting rooms are attractive and comfortable. The equipment is excellent.

The set-up in Oakland is of a similar quality and the hospital can accommodate 300 inpatients. At present it provides hospital facilities for all the Permanente units in Oakland, Richmond, and Vallejo.

The physical set-up at the Richmond Field Hospital was not as satisfactory and was overcrowded during the war years. It formerly accommodated 150 patients. It was rebuilt recently into a medical center providing outpatient care only.

#### ECONOMIC ASPECTS

During the war the program was financially successful in the Vancouver and the Oakland-Richmond area because of the large percentage (80 to 90 per cent) of sign-ups



for the Health Plan in the shipyards. The Family Health Plan which was started at a later date and required a separate registration was not quite as successful; 20 to 25 per cent of the original Health Plan members signed up their families.

It was estimated that during the war (1944) 40 per cent of the income of the Permanente Hospital in Oakland-Richmond was derived from what amounted to per capita payment, made by insurance companies, to the Permanente Foundation for the medical care of the employees of the Kaiser Shipyards for injuries incurred on the job. Only 5 to 10 per cent of the income was derived from private patients, and 50 to 60 per cent from Health Plan members. This changed considerably after V-J Day when the number of shipyard workers in Richmond decreased from 90,000 to 5 or 10,000. At present a considerable part of the income is derived from treating and hospitalizing private patients and by opening the hospital facilities to local private practitioners.

The number of patients on the Health Plan now is relatively small (20,000) but is increasing gradually from sign-up of new members drawn from the stable local population. The medical staff had to be cut 65 to 70 per cent.

The number of Health Plan members and doctors at Northern Permanente has been recently reduced very markedly. It is questionable whether the hospital will be able to continue its existence.

#### RESEARCH

Research has been done mainly in connection with clinical work. The medical department of the Oakland-Richmond hospitals has been doing significant research on the effect of double doses of sulfadiazine and penicillin in the treatment of pneumonia. The obstetrical department in Vancouver, has been doing research on the induction of labor with pituitrin and the use of spinal anesthesia in labor.

The results are published in the Permanente Foundation Medical Bulletin, a monthly magazine, and in various other medical journals.

A separate research department has just been founded in Oakland. It is supported by funds of the Foundation, the Office of Scientific Research and Development, and grants from certain drug houses. Plans are being formulated for special laboratory facilities and an animal house.

#### DOCTOR-PATIENT RELATIONSHIP

The factors that account for a good doctor-patient relationship are largely the same as in private practice. The personality of the doctor, his interest in the patient as a person, the amount of time he can spend on one patient, are of primary importance. A comfortable waiting room, friendly nurses and lay personnel, an adequate explanation if a person has to wait, a thorough examination, help to win the confidence of the patient.

It is evident from this, that one cannot make an unqualified statement about the reaction of the patients. Much depends on their individual experiences in the various departments and with the different doctors. New members are apt to be suspicious of the care offered by the Health Plan and fear that they won't get as much attention as they would get on a fee-for-service basis. Once they are acquainted with the set-up they often are impressed with the thoroughness of the care given and get a feeling of security because they are encouraged to return for further treatment whenever necessary.

Many of the complaints that came to the Health Plan Office during the war arose from an imperfect understanding of the Health Plan, its limitations and exclusions. Other complaints dealt with such matters as the waiting period, which was prolonged by checking the membership status and getting the clinical chart, referrals from one department to the other, and to being sent to the wrong department by lay personnel; the long waiting list for tonsillectomies; discourteous treatment by the receptionists; superficial care by the doctor. The majority of these complaints came from those places where the patient-burden for the doctor and the lay personnel was too great, as for example in the Richmond Field Hospital. The number of patients outgrew the facilities by far.

At the Oakland Hospital, which had the same medical staff as the Richmond Field Hospital but a much smaller census, the patients could be given a more personal treatment and they usually were quite satisfied. The inpatient care was almost invariably praised.

Some specialized departments make it their policy to have the patient come and see the same doctor at each subsequent visit to the department; this procedure is generally much preferred by patients and doctors alike.

There is a certain freedom of choice of physicians since most departments consist of a number of doctors; if a patient dislikes a particular doctor, he can request the service of another in the same department.

The Health Plan becomes especially appreciated in case hospitalization becomes necessary. There usually is no difficulty in securing bed space; the patient or family is not heavily burdened financially by the expenses that hospitalization and operation usually entail. Medical care is a known item in the budget of the patient.

People often resent the fact that doctors urge them to come to the hospital when they feel ill instead of visiting them at home; but when it is explained to them that all facilities for diagnosis are better and more readily available at the hospital they usually do not object.

#### ADVANTAGES AND DISADVANTAGES TO THE DOCTOR

One of the most important factors is that the doctor connected with the Permanente Foundations is able to give the patients, who are on the Health Plan, thorough and complete medical care without having to take the income of the patient into consideration. All the facilities of a fully equipped modern hospital are at his disposal. Most of the outpatient departments are under the same roof with the hospital facilities.

The doctor can promote his own development by the constant association with colleagues in his own and other fields, the teaching of interns and residents, and frequent staff conferences. Due to the abundance of patient material there is opportunity for specialization.

The physician can have fairly regular hours, take turns on night calls, and is insured of a definite though limited income, independent of the number of patients he sees.

The fact that he is working with a group makes him subject to problems that arise in any organization. He must follow certain rules and regulations, be able and desire to cooperate with other people, professional as well as lay personnel, and also with the administration. This is not always easy.

The security on the job depends not only on his professional ability but also on his relationship with colleagues, nurses, and patients; it is influenced by the growth or decline of the organization, by competition with doctors within the organization, and with outside doctors seeking employment at Permanente.

A factor of much controversy is the wish of the doctors to have more than advisory capacity in the administration. Most doctors feel that they want to have a more direct participation in decisions relating to the policies and financial operations of the organization.

There is no contract between the doctors and the Foundations so that employment can be and has been terminated whenever deemed advisable by the administration.

In view of the various advantages and disadvantages mentioned, it is evident that, whether a doctor likes to be connected with Permanente, depends largely on his personality, sense of values, and the importance he attaches to the aims of the organization.

Quite a few physicians were connected with Permanente because it was considered war work. After V-J Day many doctors left the organization to retire or to go in private practice, others were asked to leave because the Foundation could no longer afford to employ them due to the drop in the number of patients. Most of the physicians that remained desire to carry on this type of medical practice and hope that the necessary improvements will be made in the future.

#### SUMMARY AND CONCLUSIONS

1. The Permanente Foundations were organized during the war to provide medical care to the employees of the Kaiser shipyards and their families. The Permanente Health Plan

is based on the principles of group practice, prepayment, and adequate facilities. Recently the Plan became available to groups and individuals not connected with the Kaiser organizations.

2. Medical care at the Permanente Foundations is also available on a fee-for-service basis to people who are not members of the Health Plan. Since V-J Day the hospital facilities of the Oakland Permanente Hospital have been open to local private practitioners.

3. The cost of the Oakland-Richmond Family Health Plan is at present 60 cents to the subscriber, the same for spouse, 35 cents for one child, and 70 for two or more children. These charges proved to be more than a family of the middle-class income group can afford to pay. A less expensive plan has recently been offered whereby full coverage is given to the subscriber only, the family members are taken care of on a fee-for-service basis at reduced rates.

4. In order to make a group health prepayment plan economically feasible it is necessary to have a very large membership. The problem at present is to attract a sufficient number of subscribers from the permanent local population. The existing economic insecurity, migration, and unemployment make this difficult.

5. The majority of the patients are satisfied with the care given on the Health Plan. The public at large usually does not grasp the advantages unless they have been carefully explained.

6. The doctors employed at Permanente have the advantages of fairly regular working hours and a steady income, ready access to medical facilities, and consultations with other specialists on the staff, and an opportunity to practice medicine without a great financial barrier between the doctor and the patient. Most doctors feel that they would be more satisfied if their position would be more secure and if they would have more than advisory capacity in the administration.

#### REFERENCES

1. Stewart, Frank A., and Rieke, Robert G.: Northern Permanente, the Plant and the Institution. *Hospitals* 17: 25, 1943.
2. Garfield, Sidney R.: First Annual Report of the Permanente Foundation Hospital, Permanente Found. M. Bull. 2: 35, 1944.
3. Garfield, Sidney R.: Health Plan Principles in the Kaiser Industries, *J. A. M. A.* 126: 337, 1944.
4. Garfield, Sidney R.: Second Annual Report of the Permanente Foundation Hospital, Permanente Found. M. Bull. 3: 31, 1945.

2226 HASSE STREET.

Proof sheets of the Permanente Foundation article were sent to Dr. Clifford Sweet, asking him if he or any other pediatricians in Oakland would care to comment on the Permanente plan. The following letter was received from Dr. Sweet which we are publishing with his permission.

EDITOR.

DEAR DR. VEEDER:

In answer to your letter of July twelfth, concerning the Permanente Foundation, I can see but slight objections to the article as it appears. I have discussed the situation with two or three of the other pediatricians who worked for them for a time. They tell me that the organization is essentially as it is described here. All of these people worked there during the war and seemed to resent principally the lack of personal freedom. So far as the pediatricians are concerned, they have taken well-trained people. I was present at the recent board meeting when the chief pediatrician, Dr. Hatoff, was a candidate. He passed with flying colors.

There are two points concerning the advantages and disadvantages for the doctors that I seriously question. One is the sentence, "Due to the abundance of patient material there is opportunity for specialization." So far as I can learn from talking with the people who have been there, there is no opportunity for specialization, except for what one gains from experience.

The other is that the physician "is insured of a definite though limited income, independent of the number of patients he sees." Like any other business organization, they do not keep anyone who does not abundantly earn his keep.

I think, on the whole, they are trying to do good work and at least during the war served a very useful purpose. Because of the laboratory and other facilities, they did much better work than was done by the average practitioner. In my mind, it is entirely possible that they are pointing the way to more general use of groups in the practice of medicine.

All of the members of the active staff at Permanente are young physicians who have just passed their Boards or are awaiting eligibility. This thought was first brought to my mind when a father brought his infant to me saying he became uneasy at Permanente because there isn't a physician at Permanente who is not very young. Upon further inquiry, I find this to be so. It at once becomes apparent that medicine can be practiced at a small cost if only young physicians at a small salary are employed.

Sincerely,

CLIFFORD SWEET, M.D.

Oakland, California

# Academy News and Notes

## REPORT OF THE TREASURER

STATEMENT OF RECEIPTS AND DISBURSEMENTS, JULY 1, 1945, TO JUNE 30, 1946

Balance in checking account, July 1, 1945	\$ 344.33
Balance in savings account, State Bank & Trust Company	3,838.72
Balance in savings account, First National Bank & Trust Co.	1,544.61
	<u>\$5,727.66</u>

### Receipts:

Dues		\$28,774.11	
Wartime Assessment		6,812.50	
Exhibits—January, 1946 Meeting	\$8,230.00		
November, 1946 Meetings	4,732.50	12,962.50	
	<u></u>		
Initiation Fees		4,325.00	
Interest Earned		984.71	
Pamphlets—Child Health Record	432.31		
Immunization Procedures	434.60		
Vitamins	18.80	\$85.71	
Subscriptions—Men in service		917.25	
Committee—Post-War Courses		10,000.00	
Bonds sold		10,000.00	75,661.78
		<u></u>	<u>\$81,389.44</u>

### Disbursements:

Annual Meeting—January, 1946	3,984.97		
November, 1946	124.00	4,108.97	
	<u></u>		
Bank charge and exchange		129.23	
Certificates and mounting		74.03	
Executive Board		3,403.22	
Miscellaneous		297.57	
Office supplies and equipment		225.19	
Postage		655.67	
Rent		2,752.71	
Salaries—Secretary	9,750.00		
Assistant Secretary	1,450.00		
Stenographer	2,640.00		
Office	1,543.71	15,383.71	
	<u></u>		
Stationary and printing		1,709.48	
Subscriptions		7,980.00	
Telephone and telegrams		521.30	
Travel—Secretary		495.57	
Treasurers' Bonds		85.00	
Expense—Region I	402.60		
Region II	10.00		
Region III	86.91		
Region IV	36.94		
Region V	2,054.40	2,590.85	
	<u></u>		
Expense—States (Region I)	77.24		
(Region II)	30.26		
(Region III)	52.27		
(Region IV)	18.59	178.36	
	<u></u>		

Expense—Committees			
Cooperation with American Legion	395.21		
Legislation	25.00		
Post-War Courses	1,507.93		
Post-War Planning	17,348.52		
Rheumatic Fever	100.00		
Special	22.05	19,398.71	
	<hr/>		
Pamphlets—Child Health Record	407.66		
Immunization Procedures	28.96		
Vitamins	.78	437.40	60,426.97
	<hr/>	<hr/>	<hr/>
Balance—June 30, 1946			\$20,962.47
Balance in checking account, June 30, 1946			\$11,187.49
Balance in savings account, State Bank & Trust Company			8,214.89
Balance in savings account, First National Bank & Trust Co.			1,560.09
			<hr/>
			\$20,962.47

# News and Notes

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## CAMPAIGN TO COMBAT HEART DISEASE

The initiation of a nationwide program of public education and information on diseases of the heart was announced by officials of the American Heart Association, Inc.

The program, according to Dr. Howard F. West of Los Angeles, president of the association, will have as its prime purpose "the dissemination of educational information to the public in a broad effort to retard the rapid increase of heart disease throughout the nation."

Officials of the American Heart Association state that the association's program will call for emphasis on educational work with schools, parent-teachers' associations, and other groups concerned with children because of the importance of rheumatic fever and heart disease. According to recent surveys, this scourge of children causes more than five times as many deaths as the combined total of deaths from infantile paralysis, scarlet fever, diphtheria, measles, meningitis, and whooping cough. It is a serious disease among adults, too, as illustrated by the estimated 40,000 veterans who acquired the disease during their recent military service. The war forcibly dramatized the need for a national health program designed to retard the increase in heart disease cases. An estimated 10 per cent of the men rejected by the United States Selective Service were disqualified because of cardiovascular diseases (diseases of the heart and blood vessels).

The educational campaign of the American Heart Association will reach its climax during National Heart Week to begin on February 9, 1947, which includes St. Valentine's Day. It is expected that all branches of medicine, pharmacy, insurance, industry and many other groups interested in health and public welfare will cooperate fully.

Supporting and cooperating groups will include the following national organizations which comprise the American Council on Rheumatic Fever of the American Heart Association:

- American Academy of Pediatrics
- American Association of Medical Social Workers
- American College of Physicians
- American Hospital Association
- American Medical Association
- American Nurses Association
- American Public Health Association
- American Rheumatism Association
- American School Health Association
- National Organization for Public Health Nursing
- National Society for Crippled Children and Adults

The collaboration of the United States Public Health Service, National Tuberculosis Association, and others is expected.

Local Heart Associations and Affiliated groups in such cities as New York, Washington, Chicago, Boston, will assist in the national campaign.

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## Original Communications

### THE DETECTION OF SUSCEPTIBILITY TO WHOOPING COUGH

#### I. INSTITUTIONAL EXPERIENCES WITH THE PERTUSSIS AGGLUTINOGEN AS SKIN TEST REAGENT

HARRIET M. FELTON, M.D., AND EARL W. FLOSDORF, PH.D.  
PHILADELPHIA, PA.

VACCINATION against whooping cough has become a procedure of established worth,<sup>1-3</sup> although much remains to be learned and applied before pertussis vaccines can attain their maximal value. A simple and reliable means to aid in determining whom to vaccinate in anticipation of probable exposure becomes, therefore, a very practical need. Pertussis agglutinin has been described and trials of this material as a skin test reagent for susceptibility to whooping cough have been reported during the past few years.<sup>4-9</sup> A summary of certain clinical investigations in the field are presented in this paper, together with a description of the use of agglutinin in several institutional epidemics of pertussis.

#### REVIEW OF CLINICAL INVESTIGATION

Clinical trials of materials for skin tests in human beings were begun by using small doses of purified agglutinin in known immune individuals.<sup>7</sup> This group included donors previously hyperimmunized with pertussis vaccine at the Philadelphia Serum Exchange. Reactions were obtained which resembled those found in immunized animals. The reactions appeared as early as one-half hour after injection, were often present at twenty-four hours but had usually disappeared by thirty-six or forty-eight hours. Agglutinin has been standardized in terms of arbitrarily chosen units based on assay by adsorption of agglutinins from immune serum. One unit contains approximately 2 to 3  $\mu$ g. of solids. After considerable preliminary work, the dose for clinical use was placed at 10 units of agglutinin in 0.1 ml. normal saline. This material produced no reaction in babies between 6 and 12 months of age who had never had whooping cough or been immunized against it. In the early work, many of the reactions were checked by serum agglutination against phase I *Hemophilus pertussis* before and after the skin test. Invariably, in individuals showing an immune

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type of reaction, even if there were no circulating agglutinins detected before the test, there was a marked rise in titer following the test.

The following system of grading the reactions was established after many individuals with known histories had been tested with consistent results:

*PI—Positive-Immune:* A well indurated reaction (with or without erythema) 20 mm. or more in diameter at either one-half hour or twenty-four hours or both.

*WPI—Weakly-Positive-Immune:* An indurated reaction (with or without erythema) not exceeding 20 mm. in diameter at either one-half hour or twenty-four hours, but at least 10 mm. in diameter at either time or both.

*NS—Negative-Susceptible:* No indurated reaction at either one-half hour or twenty-four hours beyond an area 10 mm. in diameter.

It was decided to use babies in the 6- to 12-month age group as normal controls for the clinical study. The histories could be more accurately obtained in this group, and exposure would probably result in a recognized case of the disease rather than in a subclinical case of whooping cough which might give confusing results in skin testing. Further work showed that this plan was practicable.

In the early work, various substances were considered and some used for skin test controls. In some instances, a very weak dilution of horse serum was used to check a few questionable reactions. This material was chosen because horse blood had been used in the medium on which the organisms were grown. It was felt that some sensitive individual might show a nonspecific reaction to the preparation even though routine laboratory tests such as complement fixation and precipitin reactions showed no detectable amount of horse serum to be present. In about 2,000 individuals tested by these laboratories in a period of four years, only three gave much larger reactions quite different from the usual immune reaction. The intradermal injection of a very small dose of horse serum in these three children gave similar large reactions. In contrast to the material from organisms grown on horse blood, there has been no atypical reaction observed from the use of agglutinin prepared from organisms grown on media containing human blood.

As the clinical study progressed, each group tested produced reactions which agreed with accurately known histories. It was noted, however, that many older children with negative or questionable histories gave immune or weakly immune types of reaction. In all these cases the agglutinin reaction after the test showed the presence of antibacterial antibodies. This finding seems to agree with the known augmentation in responsiveness to immunizing antigen as the result of exposure or subclinical infection. A paper by Miller and associates<sup>10</sup> suggests such responses to antigenic stimuli.

During the course of the clinical investigation, the value of the skin test with agglutinin as an index of susceptibility became more evident, and, in addition, the results obtained from the serum agglutinations suggested that the material had a second and very important potentiality as a "recall" dose in all individuals with any existing immunity. The possibility of the use of agglutinin in primary immunization has not been ignored.

## EPIDEMIC IN NEW ENGLAND PEABODY HOME FOR CRIPPLED CHILDREN—INSTITUTION A

The first epidemic to be studied occurred in February, 1942, at the New England Peabody Home for Crippled Children. There were seventy-six children in the hospital at the beginning of the study. The ages ranged from 4 to 14 years and all the patients had diagnoses of chronic bone or joint disease. In reviewing the past histories it was noted that most of the patients had spent a major part of their lives in institutions. Their hospital charts represented summaries of previous institutional care with meager notes on immunization and contagious diseases. It was felt, therefore, that the past history of whooping cough or previous immunization was not entirely dependable. Two children with strong allergic histories were not included in the study.

There were nine patients with clinical whooping cough present in the hospital at the beginning of the study. These children had been isolated together in one wing of their ward. As soon as the study was started, the children with whooping cough were returned to their regular ward positions. An adequate supply of human hyperimmune pertussis serum was available if needed for the treatment of any secondary cases.

The buildings which house the patients in this institution are not modern. The wards are long and are not partitioned. The ambulatory patients mingle closely in classrooms and at meal hour, and the bed patients are put out on open porches during most of the day.

The study began in February, 1942, and was continued over a period of ten months. On the first day, measures were taken to establish a bacteriologic diagnosis of whooping cough. Hyperimmune pertussis serum was administered in the most severe cases, and the entire population of the hospital was skin tested. The treated cases responded to the serum by cessation of vomiting and decrease in the number of paroxysms.

Nasopharyngeal cultures were taken from the nine children who were isolated with whooping cough. Four of these had simultaneous exposure to cough plates with nasopharyngeal swab in place. The cultures were taken after the method described by Bradford and Slavin.<sup>11</sup> The swabs were planted immediately on Bordet-Gengou plates fortified with 30 per cent fresh horse blood. The cough plates were made from the same medium. The positive cultures were identified and confirmed by the use of high titer rabbit serum against phase I *H. pertussis*.

TABLE I. BACTERIOLOGIC CONFIRMATION OF WHOOPING COUGH IN INSTITUTION A

CULTURES	ORIGINAL CASES	SECONDARY CASES
Total nasopharyngeal swabs	9	4
Number positive for phase I <i>H. Pertussis</i>	3	1
Total cough plates	4	0
Number positive for phase I <i>H. Pertussis</i>	0	0

Table I is a summary of the results of the bacteriologic procedures which confirmed the clinical diagnosis of pertussis. Seven of the children with whooping cough were given the first dose of 20 c.c. of hyperimmune pertussis serum intramuscularly. The treatment was continued for two more doses at two-day

intervals. Two children with no evidence of existing or impending whooping cough were given serum by the same schedule in order to note the effect of the serum on the results of the skin tests and the antibody responses.

Seventy-four children were given 10 units of agglutinin in 0.1 ml. normal saline intradermally on the first day of the study. The results were read one-half hour and twenty-four hours after the test. Forty-five of these children had a blood sample drawn before the skin test for serum agglutination. These tests were performed after the method described by Flosdorf and associates.<sup>12</sup> The antigen was prepared from lyophilized cultures of phase I *II. pertussis*, strain 484, which was the same strain used in the preparation of the agglutinin. With each series of agglutinations a few samples from a preceding bleeding were used to check the reproducibility of the results. The different lots of antigen used throughout the study were tested against several sera of known potency.

No control material was used during this series of skin tests except in the case of one child who had an entirely different reaction from the usual result obtained. After a one-month interval, tests of 0.1 ml. of a 1:700 dilution of horse serum, and 0.1 ml. of a 1:10 dilution of rabbit, sheep, bovine, and human serum were given to this child. All were negative except the horse serum test, which closely resembled the original skin reaction. This child subsequently developed whooping cough.

Throughout the study, frequent blood counts were made by the resident technician on all children with suspicious coughs. The secondary cases were diagnosed entirely by shift of the blood picture and clinical findings of progressive paroxysmal cough.

The second part of the investigation was carried out approximately one month after the study was begun. Nasopharyngeal cultures were taken from four children considered to have secondary cases of whooping cough, but only one culture was positive. All of the children who had had original blood samples taken were bled again for serum agglutination.

At the end of three months there had been no additional cases of whooping cough reported in the institution. All of the children who had had original blood samples taken were bled again for serum agglutination. Skin tests were repeated on a few children from each group determined by the original skin testing. Ten months after the beginning of the study, blood samples were obtained from thirty-four of the original children who were still patients in the hospital.

*Results.*—Table I shows the bacteriologic findings in Institution A. Three positive cultures were obtained from nasopharyngeal swabs of the nine original cases of whooping cough. Simultaneous exposure of four of the children to cough plates resulted in no positive cultures. One month later, nasopharyngeal cultures were taken on four other children who had developed coughs. One of these was positive.

Table II indicates the incidence of secondary cases in relation to the reactions of the skin tests observed at the beginning of the study. The secondary

cases all occurred in children who showed susceptible or weakly immune reactions at the beginning of the study. It will be noted that immune or weakly immune reactions were observed in most of the children who had whooping cough when the study began. The disease was well established in these children so that anti-bacterial agglutinins had probably been produced. Because of the close correlation between the skin test reaction and the production of a detectable agglutinin titer fairly early in the disease, purified agglutininogen is not helpful in making an early diagnosis.

TABLE II. RELATIONSHIP OF INCIDENCE OF WHOOPING COUGH TO SKIN TESTING RESULTS IN INSTITUTIONAL EPIDEMICS

INSTITUTION	INCIDENCE OF WHOOPING COUGH	SKIN TEST REACTIONS			TOTAL
		NS	WPI	PI	
A	Original cases	1	5	3	
	Secondary cases	6	2	0	
	Total tested	34	21	19	74
B	No original or secondary cases (Control for Institution A)	0	21	33	
	Total tested	0	21	33	54
C*	Original cases	0	1	0	
	Secondary cases	5	0	0	
	Total tested	28	13	2	43

\*The chances that all the observed secondary cases could fall by random distribution into the groups indicated in Institution A and C are, respectively, less than 1 in 19 and less than 1 in 15. However, the figures on Institution C may have been altered by the fact that the susceptible children were placed in the ward by chance in proximity to the patient with whooping cough.

These figures were analyzed through the kindness of Dr. T. N. Harris of Philadelphia. NS, Negative-Susceptible; WPI, Weakly-Positive-Immune; PI, Positive-Immune.

Table III has been compiled primarily to show the correlation between the first skin test reactions and agglutinative titer taken before and at various periods after the original skin test. All but one of the children showing a susceptible skin reaction were found to have no agglutinins for *H. pertussis* at the time of the first skin test, while those with weakly immune or immune type of reaction ranged in agglutinin titer from 0 to 1:640. Titers determined one month later showed a marked increase in most children who had had any immune skin reaction. Also, a few children with no response to the skin test later showed the presence of agglutinins. The second skin test given at three months produced an immune reaction in some of the children who previously had had only a weakly immune type of reaction. In a majority of the children with previously negative-susceptible reaction this second skin test produced a weakly immune or immune reaction. Titrations of agglutinins performed at three months after the beginning of the study showed some decrease in titer, although in a few instances there was an increase. However, the tenth-month titrations showed an increase of agglutinins in practically every child. The antigenic nature of the skin test material, that is, its ability to elicit an agglutinin titer, is thus demonstrated.

The children who received control doses of hyperimmune serum failed to show any difference in either skin test reaction or agglutinative response.

The results of the agglutination tests one month after the first skin test (Table III, T<sub>2</sub>) showed such an increase in titer that the question arose as to

TABLE III. SUMMARY OF RESULTS IN INSTITUTION A (SKIN TESTING AND TITRATION FOR AGGLUTININS)

CASE NO.	SR <sub>1</sub>	T <sub>1</sub>	T <sub>2</sub>	SR <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	
1	PI	1:640	1:1,280	PI	1:640	1:5,120	
2	PI	0	0	Δ	320	40	
3	PI	20	640	PI	320	5,120	
4	PI	320	1,280	PI	320	2,560	*Negative culture, 60 c.c. serum
5	PI	20	5,120	Δ	640	2,560	
6	PI	0	0	Δ	80	1,280	**Horse Serum positive reaction
7	PI	0	320	Δ	80	160	Positive culture, 60 c.c. serum
8	PI	0	40	Δ	40	640	
9	PI	20	320	Δ	80	640	
10	PI	80	1,280	Δ	160	1,280	
11	PI	0	5,120	Δ	640	2,560	
12	PI	320	1,280	Δ	-	2,560	*Negative culture, 60 c.c. serum
13	WPI	0	0	Δ	0	0	
14	WPI	0	0	Δ	40	640	**
15	WPI	40	10,240	PI	2,560	2,560	
16	WPI	160	640	Δ	1,280	2,560	
17	WPI	0	0	Δ	0	320	
18	WPI	80	160	WPI	80	2,560	*Positive culture, 60 c.c. serum
19	WPI	0	5,120	Δ	1,280	2,560	
20	WPI	0	160	Δ	-	2,560	**
21	WPI	80	1,280	Δ	-	10,240	
22	WPI	80	640	Δ	-	-	*Negative culture
23	WPI	0	160	PI	20	1,280	
24	WPI	40	640	Δ	320	2,560	
25	WPI	-	-	Δ	-	-	*Positive culture, 80 c.c. serum
26	WPI	-	-	Δ	-	-	*
27	WPI	-	-	Δ	-	-	*
28	NS	0	0	NS	0	0	
29	NS	80	5,120	PI	2,560	5,120	
30	NS	0	40	WPI	20	160	Given serum for control
31	NS	0	0	WPI	160	-	**
32	NS	0	0	WPI	40	640	**
33	NS	0	0	NS	0	40	
34	NS	0	0	NS	0	-	
35	NS	0	5,120	WPI	1,280	2,560	
36	NS	0	0	WPI	0	40	
37	NS	0	160	WPI	40	2,560	Given serum for control
38	NS	0	0	NS	0	320	
39	NS	0	0	WPI	20	2,560	
40	NS	0	0	WPI	20	2,560	**
41	NS	-	-	Δ	-	-	*
42	NS	-	-	Δ	-	-	**Positive culture
43	NS	-	-	Δ	-	-	**

titer. Samples of serum from T<sub>1</sub> were included in each series of titrations and showed original

\*Original cases of whooping cough.

\*\*Secondary cases of whooping cough.

SR<sub>1</sub> First skin test reaction (at beginning of study).

SR<sub>2</sub> Result of second skin test (three months after SR<sub>1</sub>).

T<sub>1</sub> Agglutinative titer original.

T<sub>2</sub> Agglutinative titer 1 month after beginning of study.

T<sub>3</sub> Agglutinative titer 3 months after beginning of study.

T<sub>4</sub> Agglutinative titer 10 months after beginning of study.

Δ Not given a second skin test.

0 In agglutinative titer column means <1:20.

NS, Negative-Susceptible; WPI, Weakly-Positive-Immune; PI, Positive-Immune.

whether this was caused by the skin test antigen, the presence of whooping cough in the institution, or by both factors. An attempt to answer this question was made by carrying out skin test and agglutination studies on children in another institution in which there was no whooping cough present.

TABLE IV. SUMMARY OF RESULTS IN INSTITUTION B (SKIN TESTING AND TITRATION FOR AGGLUTININS)

CASE NO.	SR	T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>
1	PI	0	1: 20	1: 40	1: 80
2	PI	0	640	320	640
3	PI	1:80	10,240	2,560	10,240
4	PI	0	1,280	1,280	1,280
5	PI	40	10,240	2,560	5,120
6	PI	0	1,280	640	640
7	PI	0	2,560	2,560	5,120
8	PI	160	2,560	2,560	5,120
9	PI	0	80	80	320
10	PI	0	5,120	2,560	2,560
11	PI	0	1,280	1,280	640
12	PI	0	5,120	1,280	1,280
13	PI	0	160	160	320
14	PI	0	1,280	640	-
15	PI	640	10,240	2,560	-
16	PI	0	10,240	2,560	-
17	PI	20	2,560	1,280	-
18	PI	0	5,120	2,560	-
19	PI	80	10,240	2,560	-
20	PI	0	5,120	1,280	-
21	PI	0	2,560	2,560	-
22	PI	0	40	80	-
23	PI	0	1,280	640	-
24	PI	0	160	160	-
25	PI	0	20	160	-
26	WPI	0	40	0	80
27	WPI	0	2,560	2,560	5,120
28	WPI	0	160	160	1,280
29	WPI	0	0	320	40
30	WPI	-	1,280	1,280	640
31	WPI	0	160	160	160
32	WPI	80	5,120	2,560	10,240
33	WPI	0	160	80	320
34	WPI	0	40	40	40
35	WPI	0	5,120	1,280	640
36	WPI	0	5,120	2,560	1,280
37	WPI	0	2,560	1,280	2,560
38	WPI	?	10,240	2,560	-
39	WPI	0	320	320	-
40	WPI	0	160	160	-
41	WPI	0	0	0	0
42	WPI	0	2,560	1,280	-
43	WPI	0	5,120	2,560	-

SR Skin test reaction (at beginning of study).

T<sub>1</sub> Agglutinin titer before skin test.T<sub>2</sub> Agglutinin titer one month after skin test.T<sub>3</sub> Agglutinin titer three months after skin test.T<sub>4</sub> Agglutinin titer ten months after skin test.

0 Agglutinin titer less than 1:20.

CONTROL GROUP AT CHILDREN'S HEART HOSPITAL OF PHILADELPHIA—  
INSTITUTION B

This control study was done in the Children's Heart Hospital of Philadelphia. This is a hospital for the care of children convalescing from rheumatic fever, with approximately sixty children as patients. The group is divided into two large open wards with one floor for boys and one for girls. There are approximately thirty children in each section. The ambulatory children mingle in schoolrooms and at meals. There was no case of whooping cough in the institution at the time of the study, nor had there been any known exposure to it.

The original skin testing and serum titrations in this hospital were performed ten days later than in Institution A. Thereafter the studies were made concurrently. There were no repeated skin tests done in this institution, as all the original tests showed the immune type of reaction. The results are shown in Table II, Institution B.

Table IV shows the skin test results and agglutinin titrations at the Children's Heart Hospital of Philadelphia. The original absence or low titer of agglutinins in the presence of immune reactions to skin tests are shown also in this group of children. A marked rise in titer one month after the skin tests is also shown in this institution where there was no whooping cough present. In general, the range of titers at one month was much higher than in Institution A, and there was less decrease of titer at the end of three months. At the end of ten months the titers had been maintained or slightly increased.

The larger number of weakly immune or immune types of reactions in the children of this hospital might be due to the fact that many of them had been vaccinated against whooping cough and, in general, the entire group had spent *more of their lives outside of a hospital than the children in the previous institution.*

#### EPIDEMIC IN ALFRED I. DU PONT INSTITUTE—INSTITUTION C

A small institutional epidemic of whooping cough was observed in the Alfred I. du Pont Institute of the Nemours Foundation, in the spring of 1943. There was one case of clinical whooping cough at the onset of the study. This child had been removed from the open ward into very complete isolation.

This institution has been built and planned so that the children are separated into small groups, and there is less intermingling than in either of the two institutions previously discussed. In the wards, although there are no partitions, there is ample space between the beds. The plan of study in this institution was similar to that already reported. A nasopharyngeal swab was taken from the child who had whooping cough in an attempt to establish the organism, with a negative result.

All the children were given 10 units of agglutininogen in 0.1 ml. of normal saline intradermally after the case of whooping cough was diagnosed. Results of the skin testing are shown in Table II, Institution C. Eight of the smaller children with the susceptible type of reaction were given hyperimmune pertussis serum for prophylaxis in about one-half the recommended dosage (20 ml. instead of 40 ml.).<sup>13</sup> Five secondary cases of whooping cough developed in this group. All of these cases developed in children who were situated near the bed of the child who had the original case. The secondary cases were all very mild and again were only diagnosed by the shifting blood counts on the children who developed coughs. Only one child of this group had a cough severe enough to cause vomiting. Agglutinin titrations were omitted in this study.

#### DISCUSSION

When clinical investigation was first begun, the individuals to be tested were chosen on the basis of history of the disease. As the work progressed,

it became evident that there were many persons without known history of whooping cough in whom immunity was demonstrated by the skin test reaction, and this immunity further indicated by serum agglutination. This immunity could have developed as the result of exposure or subclinical infection.

The apparent widespread occurrence of partial immunity as indicated by the skin test renders questionable the value of classification of results on the basis of past history. The young infants with no history of whooping cough give skin test results compatible with their history. They invariably give a negative-susceptible reaction even to large doses of agglutinin. Large numbers of serum agglutinations before and after skin testing have shown that a demonstrable titer has followed in all but a very few patients who had an initial immune skin test reaction. This rise in titer has been found at approximately the end of the first week after the skin test in any immune individual, even though agglutinins were absent before the skin test. This appears to be one of the most significant findings in these studies. The protection afforded the susceptible and weakly-positive-immune children by the skin test in Institution A is believed to have contributed to reducing the number of secondary cases. The presence of pertussis in Institution A as well as the antigenicity of the first skin test could together produce the reversal of the skin test in many individuals who were retested. Further data (to be published) show that a single skin test dose of agglutinin may produce a slight rise in agglutinin titer as well as a feeble reaction to a second skin test. A third skin test will often show a definitely positive-immune reaction with an agglutinin titer as high as 1:640 or 1:1,280.

#### SUMMARY

A purified agglutinin of phase I *H. pertussis* was used as a skin test reagent in three institutions.

An epidemic of whooping cough was studied in detail; all secondary cases occurred in children whose skin tests indicated susceptibility or weak immunity.

Routine agglutination tests indicated the value of agglutinin as a "recall" dose, as shown by the small number of cases following skin testing of the entire population of the institution.

Parallel studies were done in an institution in which there was no whooping cough, in order to rule out the effect of the presence of the disease on the skin test reaction and agglutinative titer of exposed individuals. The effectiveness of the skin test reagent as an antigen was well established by the results obtained in this control institution.

In a second institution in which one case of whooping cough appeared, all secondary cases occurred in individuals who had had negative skin tests.

We wish to express our appreciation to Dr. Gerald Hoeffel, Medical Director of the New England Peabody Home, who assisted in planning the studies in that institution, and to Dr. Ella Roberts, Medical Director of the Children's Heart Hospital of Philadelphia, by whose permission the studies there were made possible. We appreciate the assistance of Dr. Amedeo Bondi, Department of Bacteriology, Temple University School of Medicine, in making the bacteriologic studies.



## REFERENCES

1. Felton, H. M., and Willard, C. Y.: J. A. M. A. 126: 294, 1944.
2. Cravitz, L., and Cauley, J. H.: J. A. M. A. 129: 539, 1945.
3. Cohen, S. M., and Wheeler, M. W.: Am. J. Pub Health 36: 371, 1946.
4. Flosdorf, E. W., Kimball, A. C., and Chambers, L. A.: Proc. Soc. Exper. Biol. & Med. 41: 122, 1939.
5. Flosdorf, E. W., and Kimball, A. C.: J. Immunol. 39: 287, 1940.
6. Flosdorf, E. W., and Kimball, A.: J. Immunol. 39: 475, 1940.
7. Flosdorf, E. W., and McGuinness, A. C.: Am. J. Dis. Child. 64: 43, 1942.
8. Felton, H. M., and Flosdorf, E. W.: J. PEDIAT. 22: 259, 1943.
9. Flosdorf, E. W., Felton, H. M., Bondi, A., and McGuinness, A. C.: Am. J. M. Sc. 206: 421, 1943.
10. Miller, J. J., Silverberg, R. J., Saito, T. M., and Humber, J. B.: J. PEDIAT. 22: 637, 1943.
11. Bradford, W. L., and Slavin, B.: Proc. Soc. Exper. Biol. & Med. 43: 590, 1940.
12. Flosdorf, E. W., McGuinness, A. C., Kimball, A. C., and Armstrong, J. G.: J. PEDIAT. 19: 638, 1941.
13. McGuinness, A. C., Armstrong, J. G., and Felton, H. M.: J. PEDIAT. 24: 249, 1944.

# THE DETECTION OF SUSCEPTIBILITY TO WHOOPING COUGH

## II. CLINICAL STANDARDIZATION OF THE DIAGNOSTIC SKIN TEST REAGENT AND ITS USE IN INSTITUTIONAL AND IN PRIVATE PRACTICE

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CLINICAL studies of the agglutinin skin test for susceptibility to whooping cough which have been reported previously have concerned the original sonic-extracted agglutinin as described by Flosdorf.<sup>1</sup> A simplified method of preparing agglutinin by chemical extraction has been described subsequently by Smolens and Mudd.<sup>2</sup>

Preliminary laboratory trials with this acid-extracted agglutinin (referred to as E-1) indicated that it was similar to sonic-extracted agglutinin (A-1) with respect to absence of toxicity, positive skin reactions in immune animals, and ability to stimulate agglutinins against *Hemophilus pertussis*. In addition, the yield of purified agglutinin by this chemical process was greater than by the sonic method. This newly prepared agglutinin was assayed by agglutinin adsorption of high titer phase I pertussis serum, and the unit dosage was recommended from this procedure. This method of standardization has been used by Flosdorf.<sup>1</sup>

### CLINICAL STANDARDIZATION OF AGGLUTININ AS SKIN TEST REAGENT

A preliminary clinical trial was made to compare this newly prepared agglutinin with sonic-extracted agglutinin. Known immune individuals with high agglutinin titers against phase I *H. pertussis* were chosen from the donors at the Philadelphia Serum Exchange. Babies from 6 to 12 months of age with no recorded history of whooping cough were chosen for the susceptible group. Twenty-five immune donors were injected intradermally in the right arm with 10 units of sonic-extracted agglutinin in 0.1 ml. isotonic saline, and 10 units of acid-extracted agglutinin in 0.1 ml. isotonic saline was given in a similar position on the left arm. All of the reactions were observed daily for one week. The findings were uniform in each group. The immune donors showed an immediate reaction in one-half hour consisting of a wheal with a flare of erythema. The size of this reaction was slightly larger on the left (E-1) arm than the right (A-1). At twenty-four hours these individuals all had large reactions on both arms. There was induration and erythema, with no tenderness, on each arm. In some instances the areas measured 50 to 60 mm. in diameter. Again the total size was somewhat larger on the left (E-1) arm, the induration much more evident, and the erythema more marked. The reaction on the right (A-1) arm began to disappear after twenty-four to thirty-six hours, and there was no residual pigmentation observed in any instance. At the same time, reactions to the acid-extracted agglutinin began to fade but were evident for several days longer. In some instances faint pigmentation remained.

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Sixteen babies were tested on the same day in a similar manner with 10 units of each material. There was no reaction observed on either arm of any baby during the seven-day observation period. A few babies were then given as much as 50 units of acid-extracted agglutininogen with no skin reaction evident at any time during a similar seven-day observation period. The results of this first trial are shown in Table I.

TABLE I. SPECIFICITY OF ACID- AND SONIC-EXTRACTED AGGLUTININOGEN\* IN KNOWN IMMUNE AND SUSCEPTIBLE INDIVIDUALS

SKIN TEST REACTIONS							
	NEGATIVE-SUSCEPTIBLE		WEAKLY-POSITIVE-IMMUNE		POSITIVE-IMMUNE		TOTAL
	A <sub>1</sub>	E <sub>1</sub>	A <sub>1</sub>	E <sub>1</sub>	A <sub>1</sub>	E <sub>1</sub>	
Infants (Susceptible)	16	16	0	0	0	0	16
Adults (Immune)	0	0	0	0	25	25	25

\*Ten units of each material per 0.1 ml.

A<sub>1</sub> Sonic-extracted agglutininogen.

E<sub>1</sub> Acid-extracted agglutininogen.

Further experiments to establish a satisfactory dose of acid-extracted agglutininogen were made by performing parallel tests with sonic-extracted agglutininogen on fifty-nine children in the Children's Heart Hospital of Philadelphia. The status of immunity in many of these children had been established by a previous skin test with 10 units of sonic-extracted agglutininogen.<sup>3</sup> In this group, a comparison was made by means of 5 units of each material in 0.1 ml. of isotonic saline. It was found in several cases that this amount of sonic-extracted agglutininogen was not sufficient to produce an immune type of reaction in an individual who had previously given an immune type of reaction to 10 units of the same material. In general, the reaction to acid-extracted agglutininogen was almost twice as large in diameter as the reaction to sonic-extracted material. In many cases when both reactions were of a weakly immune type at the end of one-half hour, the reaction to the sonic material had disappeared in twenty-four hours, while that to the acid fraction was of the strongly immune type. After this series of tests it was decided to discontinue any readings earlier than twenty-four hours. Review of the skin test results up to that time indicated that all twenty-four-hour positive reactions had been positive in one-half hour also. The results of this study shown in Table II indicated that 5 units of acid-extracted agglutininogen gave satisfactory results in a group with known immunity. The intensity of the reactions after 5 units of acid-extracted agglutininogen suggested that the dosage might be decreased still more.

TABLE II. SENSITIVITY OF ACID- AND SONIC-EXTRACTED AGGLUTININOGEN\* (IN IMMUNE INDIVIDUALS)

SKIN TEST REACTIONS				
	NEGATIVE-SUSCEPTIBLE	WEAKLY-POSITIVE-IMMUNE	POSITIVE-IMMUNE	TOTAL
A <sub>1</sub> , Sonic-extracted agglutininogen	28	29	2	59
E <sub>1</sub> , Acid-extracted agglutininogen	5	19	35	59

\*Five units/0.1 ml.

A group of children from the surgical and orthopedic wards at the Children's Hospital with previous histories of whooping cough were chosen for this further testing. Four groups of five or more children were used. Each group was given one of the following doses: 2.5, 1, 0.5, and 0.25 units in 0.1 ml. of isotonic saline. The results are shown in Table III.

TABLE III. THE ANTIGENIC EFFECT OF SERIAL DOSES OF ACID-EXTRACTED AGGLUTINOGEN ON AGGLUTINATIVE TITER

CASE NO.	UNITS OF AGGLUTINOGEN	SKIN TEST REACTION	AGGLUTININ TITER BEFORE SKIN TEST	AGGLUTININ TITER ONE WEEK AFTER SKIN TEST
1	2.5	PI	1:20	1:1,280
2		PI	<1:20	1:1,280
3		PI	1:20	1:160
4		WPI	<1:20	1:640
5		WPI	<1:20	1:2,560
6		NS	<1:20	<1:20
1	1.0	PI	<1:20	1:160
2		PI	<1:20	1:2,560
3		PI	<1:20	1:320
4		PI	1:80	1:2,560
5		NS	<1:20	<1:20
6		NS	<1:20	<1:20
7		NS	<1:20	<1:20
8		NS	<1:20	1:40
1	0.5	WPI	1:80	1:640
2		WPI	<1:20	1:320
3		WPI	1:40	1:320
4		WPI	<1:20	1:80
5		NS	<1:20	<1:20
1	0.25	WPI	<1:20	1:640
2		WPI	<1:20	1:80
3		WPI	<1:20	1:160
4		WPI	1:20	1:80
5		NS	<1:20	<1:20

NS Negative-Susceptible.

WPI Weakly-Positive-Immune.

PI Positive-Immune.

These results reveal that an immune child can give a positive reaction to very small doses of E-1. From the data in this series of skin tests it was felt that one unit of E-1 could be used satisfactorily for further work. The antigenic effect of these small doses is not as great as that of larger doses. This series of cases is very small, and again shows that immunity cannot always be predicted by history alone.

#### MANAGEMENT OF AN INSTITUTIONAL EPIDEMIC

During the time that fractional doses of acid-extracted agglutininogen were being tried, another trial with simultaneous doses of acid-extracted and sonic-extracted agglutininogen was made at the Pennsylvania School for the Deaf. This institution had had an unusually severe outbreak of whooping cough in 1942, with about forty cases, and the records prior to 1942 showed that an outbreak of whooping cough had occurred almost yearly.

The children live in unusually close contact in both schoolrooms and dormitories because of their disability. There had never been a routine immunization

program against pertussis. The school records were very accurate, and the past histories were felt to be unusually reliable because parents are likely to remember illnesses in defective children quite well. These children do not lead an entirely closed institutional life but often spend week ends and long vacations with their families. It is, therefore, easy to understand the frequent incidence of pertussis in this school.

The investigation was started in this group in May, 1943, with the hope that the next outbreak of whooping cough could be better studied and controlled. One hundred sixty-one children were tested simultaneously with 10 units of sonic-extracted material and 5 units of acid-extracted material. The reactions were more nearly parallel in size than the reactions at the Heart Hospital, where 5 units of each material were used, but the intensity of the E-1 reaction was again greater. In the group which had simultaneous skin tests, twenty-three of the children predicted to be susceptible gave delayed positive reactions which appeared on about the sixth day and lasted about twenty-four hours. These reactions were similar to the immune type of reaction in other children. In all cases the secondary reaction to E-1 was as strong or stronger than to A-1 (sonic-extracted agglutinin). Forty-two immune children showed a similar delayed reaction on the sixth day. In checking the histories, it was found that many of these children had been exposed to previous epidemics in this institution but had not contracted whooping cough. The others had past histories of whooping cough. In November, 1943, the forty-six new students of the fall semester were tested with one unit of E-1, since this dosage had been demonstrated to give a satisfactory response. No delayed reactions were observed in this group. The classification of the children by the skin test results is shown in Table IV.

TABLE IV. SKIN TEST RESULTS IN PENNSYLVANIA SCHOOL FOR DEAF

GROUP	AGGLUTININ UNITS		SKIN TEST REACTIONS			
			NS	WPI	PI	TOTAL
April, 1943, residents	A <sub>1</sub>	10	47	67	47	161
	E <sub>1</sub>	5	47	67	47	161
November, 1943, new students	E <sub>1</sub>	1	31	9	6	46
April, 1944, children previously NS	E <sub>1</sub>	1	5	15	46	66

NS Negative-Susceptible.

WPI Weakly-Positive-Immune.

PI Positive-Immune.

At the beginning of December, 1943, three weeks after the new students were tested, the first case of whooping cough developed in the primary section of this institution. Skin test results were available on 207 children before the outbreak of whooping cough. Because of the possibility of starting a large epidemic, the child who first developed whooping cough was immediately withdrawn from the classroom and dormitory. In spite of the isolation of this child, four more cases developed within the next two weeks. All of these cases were among the children who were classified as susceptible by the skin test. Bacteriologic study of this epidemic resulted in four nasopharyngeal cultures showing typical phase I *H. pertussis*.

The approach of the Christmas holiday produced a crisis in the management of the institution. By special permission from the local boards of health, arrangements were made to send home all the children susceptible according to the agglutininogen skin test. By this procedure it was hoped to shorten the epidemic. The four children with secondary cases of whooping cough were allowed to continue in their normal dormitory and class routine. During the Christmas holiday, five other children developed clinical whooping cough at home. No cultures were taken. Table V summarizes the incidence of whooping cough in this group of children who had been previously skin tested. No case developed among the children remaining at school in spite of the fact that four children with proved whooping cough were put back into the school routine.

TABLE V. INCIDENCE OF WHOOPING COUGH IN RELATION TO CLASSIFICATION BY SKIN TESTING IN PENNSYLVANIA SCHOOL FOR THE DEAF

CASES OF WHOOPING COUGH ACCORDING TO SKIN TEST REACTIONS			
NEGATIVE-SUSCEPTIBLE	WEAKLY-POSITIVE-IMMUNE	POSITIVE-IMMUNE	TOTAL
10	0	0	10

In April, 1944, skin tests were performed on sixty-six of the previously susceptible children. The results showed five of them still of the susceptible type, fifteen of the weakly immune type, and forty-six to be now definitely immune. These results are shown in Table IV.

It was not possible to do routine agglutinations on this entire group. One week after the repeat skin testing in April, representative cases were chosen for serum agglutination. Three children with susceptible skin reactions were bled. In two, the agglutinative titer was negative, and in the third, the titer was 1:320. Seven children who had whooping cough in December, 1943, were bled. All of them showed immune or weakly immune skin reactions, and titers ranged from 1:20 to 1:2,560. Three children with the weakly immune type of reactions were bled and the titers ranged from 1:80 to 1:1,280. Four other children showing the immune type of skin reaction in the original testing were bled and in all instances the titer was 1:1,280 or 1:2,560.

Observation of this school group has been continued. As each semester begins, the new students are skin tested with acid-extracted agglutininogen. The susceptible ones are given routine immunization with a standard phase I vaccine. There has been no case of whooping cough in the institution since the outbreak reported in this paper.

#### COMPARATIVE SKIN TESTS WITH AGGLUTINOGEN AND WITH TOXIN

The final episode of the clinical investigation of agglutininogen was the comparison of this fraction of phase I *H. pertussis*, which demonstrates the presence of antibacterial immunity, with another material for skin testing developed by Streaun.<sup>4</sup> This material, described as a toxin, has been used for the purpose of determining the presence of antitoxic immunity. It gives a positive or primary irritative reaction in the skins of individuals with no antitoxic antibodies. Individuals with antitoxic antibodies should have no reaction to this material if it

be a pure toxin. The interpretation of these reactions is exactly opposite to the agglutinin skin test results. A summary of the expected reactions from each skin test material follows:

	SUSCEPTIBLE	IMMUNE
Agglutinin Test	negative	positive
Toxin Test	positive	negative

Early in 1945 there was an opportunity to observe the results of simultaneous skin tests using the toxin and phase I agglutinin. Children were chosen from two health centers under the direction of the Division of Maternal and Child Hygiene of the Department of Public Health of Philadelphia. The test groups were set up from Department of Public Health records under headings of (1) immunized, (2) history of whooping cough, and (3) history of no immunization or whooping cough. The tests were placed on opposite arms at the same time, one physician administering the toxin test, another, the agglutinin test. The doses were one skin test unit of toxin as defined by Stearn and one unit of acid-extracted agglutinin. All readings were made at the end of twenty-four hours.

TABLE VI. COMPARISON OF TOXIN AND AGGLUTININ SKIN TESTS

HISTORY FOR PERTUSSIS	TEST REAGENT	RESULTS			TOTAL
		IMMUNE	SUS-CEPTIBLE	DOUBTFUL	
<i>Health Center A</i>					
Vaccinated	Agglutinin	42	21	2	65
	Toxin	1	64		65
History of whooping cough	Agglutinin	3	9		12
	Toxin	2	10		12
No history of whooping cough or vaccination	Agglutinin	2	26		28
	Toxin	0	28		28
					105
<i>Health Center B</i>					
Vaccinated	Agglutinin	117	31		148
	Toxin	3	42		45
History of whooping cough	Agglutinin	1	0		1
No history of whooping cough or vaccination	Agglutinin	3	44		47
	Toxin	2	10		12
					196

At one center, 105 children were tested with both materials; at the other, 197 children were tested with agglutinin and only fifty-seven with toxin. The results shown in Table VI indicate clearly that the toxin test is of little value in any group which has been immunized with standard phase I whole pertussis vaccine. The children who gave positive-immune reactions after agglutinin also gave positive reactions with toxin test material on the opposite arm. The readings on the toxin test suggest that the expected result was confused by the presence of agglutinin in the toxin test material.

A recent paper by Cravitz and Williams<sup>5</sup> reported similar findings in a series of immunized children from Boston health centers tested for susceptibility by the toxin. These workers used heated toxin for a control test in their

study. They concluded that the large percentage of positive reactions in these immunized children must be considered to be due to the presence of agglutinin, since the toxin had been destroyed by heat.

At both centers the children with no history of whooping cough or immunization gave the large pink reaction after the toxin test. These children showed no reaction at the site of the agglutinin test. This group gave the only clear-cut reactions to the toxin test.

Analysis of the records showed that a large number of the vaccinated children with susceptible reactions had been vaccinated several years before when the vaccine used in the City Health Centers had been prepared from strains of questionable antigenicity, and the interval between the doses was shorter than that used at present. Further tests with agglutinin in groups vaccinated with later vaccines gave a much higher number of immune reactions.

#### DISCUSSION

The value of purified agglutinin in the determination of susceptibility to whooping cough has been demonstrated by reports of its use in large numbers of children.<sup>6-8</sup> The logical sequel to reports of a new biological is the appearance of more simplified and practical methods of preparing a product which will meet the specifications of the original material.

The clinical observations reported here show the evolution of a satisfactory material, dosage schedule, and reading time. The dosage set for the original sonic-extracted agglutinin was determined first in the laboratory, and then finally by trial in human beings. The predicted dose seemed to be satisfactory. Acid-extracted agglutinin was studied by the same method but had to be finally standardized in human beings because the predicted dose was stronger than the dose of sonic-extracted agglutinin determined by the same technique. At the present time the composition of agglutinin is not known. Until there has been further biochemical study of this product, standardization in human beings is probably the only satisfactory method of assay. The selection of a suitable control for this method of assay must be carefully planned. At present, new lots of agglutinin are assayed by laboratory methods and then tested in known immune individuals in order to determine the smallest dose that will give a well-defined, positive reaction. The immune status of the test individual is established by a parallel skin test with agglutinin, the potency of which has been established after long clinical study. The specificity of the reaction and the absence of toxin in any new agglutinin must be established by giving relatively large doses intradermally to susceptible infants.

The optimal time for reading the test has been placed at twenty-four hours. At first the readings were made at one-half hour, four hours, and twenty-four hours. Careful determinations of agglutinins indicated that all individuals with a positive or immune reaction which persisted for twenty-four hours showed a subsequent rise in agglutinin titer. Although many individuals showing a positive reaction at the end of one-half hour and not showing it at twenty-four hours show a rise in agglutinin titer, the danger of mistaking a nonspecific, immediate reaction in the skin for an immune reaction must be considered. The



recommended twenty-four-hour reading has been entirely satisfactory in more recent studies with agglutinin.

As a result of the experience to date, a simple classification of individuals as immune or susceptible has been adopted. An area of induration and erythema of 1 square centimeter or more, which may be present at one-half hour but must be present at twenty-four hours after the intradermal administration of one skin test dose of pertussis agglutinin, is considered an immune reaction. A reaction less than this or no reaction is considered to indicate susceptibility.

The delayed reactions which have been observed on the sixth day following doses of 5 or 10 units of agglutinin come exactly at the time when the agglutinin titer begins to rise. Correlation of past histories with the incidence of delayed reactions indicates that individuals with "contact immunity" may show this reaction. Ratner's theory<sup>9</sup> of local serum sickness may explain this phenomenon.

Comparison of the agglutinin test with the Strean toxin test gave clear demonstration of the unsatisfactory results obtained with this toxin in attempting to evaluate the immune status of any group which had been vaccinated with standard phase I whole pertussis vaccine. The toxin test gave the expected reaction only in the susceptible children. Two reasons may be suggested to explain the unsatisfactory reactions seen in the vaccinated children. If traces of agglutinin were present in the toxin, the positive reactions seen in the children predicted by agglutinin to be immune would be explained. In the susceptible children, the presence of agglutinin in the testing material would not interfere with the primary toxic reaction which indicates susceptibility by the toxin test. The work of Cravitz and Williams<sup>5</sup> shows that after immunization even with a vaccine combined with toxoid, very little or no circulating antitoxin can be detected after six months. Therefore, the toxin test cannot be expected to measure immunity in any population immunized with standard vaccines.

Agglutinin has been used in private practice as part of the routine for preschool examination. It is of double value in demonstrating the existence of immunity to pertussis several years after primary immunization, and in stimulating that immunity. If the child seems to be susceptible, another course of immunization is given. In this way it may be possible to prevent the occurrence of pertussis in the older children by maintaining more adequately the immunity after primary vaccination.

#### SUMMARY

The agglutinin of phase I *H. pertussis* prepared by a method of chemical extraction has been compared with the sonic-extracted material which has been shown to be a satisfactory skin test agent for susceptibility to pertussis.

The acid-extracted agglutinin was standardized against the sonic product and found to be more potent, and to give more clear-cut reactions.

Review of these data showed that a twenty-four-hour reading time could be recommended.

At present the skin test dose is estimated in units by laboratory methods, and assayed finally by human intradermal inoculation.

This agglutinin gives identical results to those obtained with the sonic-extracted material; there is no reaction even in large doses in normal (susceptible) individuals, and an allergic reaction at the site of injection in any individual with solid immunity to whooping cough from either immunization or previous attack of the disease.

In an institution with annual outbreaks of whooping cough, the use of agglutinin before the anticipated epidemic was followed by a significant decrease in the number of cases, all of which occurred in the group predicted by the skin test to be susceptible. Yearly skin testing of new students followed by immunization of all susceptible children has resulted thus far in the absence of whooping cough from this school.

Comparison of the agglutinin skin test with the Streaan toxin test in children from City of Philadelphia Health Centers has been made. The results clearly indicated a close correlation between the history and the agglutinin skin test results. On the other hand, results from the use of the Streaan test revealed that satisfactory correlation between history and toxin test only existed in the group of known susceptible children.

The use of agglutinin has a definite place as a public health measure in periodic examinations of young children. The duration of primary immunization may be determined while the antigenicity of agglutinin produces a prompt recall of any existing antibacterial immunity.

We acknowledge with gratitude the cooperation and continued interest of the medical board and teaching staff of the Pennsylvania School for the Deaf. The work in the city health centers of Philadelphia was carried out by the permission of Dr. Harriet L. Hartley and Dr. Dorothy Wood. Miss Elsie Robbins, principal bacteriologist of the Department of Laboratories of the City of Philadelphia, assisted in analyzing these data obtained in the city health studies.

#### REFERENCES

1. Flosdorf, E. W., and Kimball, Anne C.: *J. Immunol.* 39: 475, 1940.
2. Smolens, Joseph, and Mudd, Stuart: *J. Immunol.* 47: 155, 1943.
3. Felton, Harriet M., and Flosdorf, Earl W.: *J. PEDIAT.* 29: 677, 1946.
4. Streaan, L. P.: *Canad. M. A. J.* 42: 525, 1940.
5. Cravitz, L., and Williams, J. W.: *J. PEDIAT.* 28: 172, 1946.
6. Flosdorf, E. W., Felton, H. M., Bondi, A., and McGuinness, A. C.: *Am. J. M. Sc.* 206: 421, 1943.
7. Felton, Harriet M., and Flosdorf, Earl W.: *J. PEDIAT.* 22: 259, 1943.
8. Sauer, L. W., and Markley, R. N.: *J. A. M. A.* 131: 967, 1946.
9. Ratner, Bret: *Allergy, Anaphylaxis and Immunotherapy*, Baltimore, 1943, Williams & Wilkins, p. 423.

## HYPOFUNCTION OF THE ADRENALS IN EARLY LIFE

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IN THE newborn period and early weeks of life there are observed not infrequently certain symptoms resulting from hormonal imbalance and some apparent difficulty in adjustment of the endocrine mechanism by the infant. Familiar examples are: (1) Physiologic lactation, menstruation, and involution of the uterus of the newborn due to the placental transmission of estrogen and prolactin to the infant's circulation from the mother; (2) hypoglycemia and hyperinsulinism of the newborn which we have discussed in detail previously;<sup>1</sup> and (3) a low calcium tetany apparently due to a physiologic hypoparathyroidism resulting from a maternal hyperparathyroidism that is physiologic during pregnancy.

Most of these disturbances are transient, although occasionally the symptoms may persist for several weeks. Analogous symptoms referable to abnormal hormonal activity of the adrenal glands, except for the serious acute symptoms of adrenal hemorrhage (Waterhouse-Friderichsen syndrome) and rare cases of macrogenitosomia and pseudohermaphroditism associated with symptoms and signs of Addison's disease,<sup>2-4</sup> have not been recognized as a clinical entity. It is the purpose of this paper to present certain clinical observations which give support to the view that hypofunction of the adrenal cortex at times may produce disturbances in the metabolism of young infants.

Interest in the possibility of recognizing symptoms of adrenal cortical insufficiency in certain infants was stimulated by the author's recent observation of an infant with Addison's disease in whom a pronounced tendency to dehydration, asthenia, weight loss, hypoglycemia, anorexia, intermittent vomiting, and loose stools were the prominent symptoms.<sup>5</sup> Such symptoms in young infants are not infrequent and may result from a number of causes.

There is a small group of apparently physically normal premature and full-term infants frequently referred to as "constitutionally inferior" because of inability to thrive despite adequate medical and nursing care. This type of infant is usually weak, takes food reluctantly, and may manifest some or all of the symptoms exhibited by patients with Addison's disease. The pathologist is usually of no assistance in determining the cause of these "metabolic" deaths. This is the type of patient which we thought might be benefited by the administration of adrenal hormones.

Much progress has been made in understanding the physiologic function of the adrenal cortex from work on experimental animals and the study of Addison's disease. Loeb<sup>6</sup> showed that the sodium levels may be low and the potassium levels high in Addison's disease. It is generally known that there is a decreased ability of the renal tubules to reabsorb sodium, and, as a result, there is a decreased concentration of sodium in the blood, a corresponding fall in blood bi-

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carbonate, chloride, or both, increase in plasma protein, decrease in plasma volume, decrease in rate of blood flow, increase in excretion of chloride, steady loss of weight, dehydration, refusal of food, vomiting, increase in nonprotein nitrogen, muscular weakness, and anuria when shock is extreme.

Normal intestinal function may be to a great extent dependent upon the activity of the true cortex. After removal of the adrenals in experimental animals, anorexia may be pronounced. In addition, there may be a tendency to intermittent intestinal upsets with vomiting, diarrhea, or both. These complaints are part of the picture in Addison's disease.<sup>7</sup> Many animal experiments<sup>8-13</sup> have demonstrated that adrenalectomy markedly impairs the intestinal absorption of water, glucose, sodium chloride, and potassium, and alters the ability of the body membranes to maintain proper gradients of concentration of certain salts. Tuerkischer and Wertheimer,<sup>14</sup> in their experiments on adrenalectomized rats, and Thaddea,<sup>15</sup> in his study of the gastric secretions in patients with Addison's disease, indicated that the secretion of rennin, pepsin, and hydrochloric acid is dependent upon normal adrenal function.

The adrenal cortex has a significant part to play in carbohydrate metabolism. Cori and Cori<sup>16</sup> and Britton and Silvette<sup>17</sup> effectively demonstrated depletion of liver glycogen and consequent hypoglycemia in adrenalectomized animals. Most physiologists feel that the adrenal cortical hormones cause decreased utilization of glucose with a consequent rise in blood sugar; however, this theory has not been definitely proved. It is agreed that the hormones increase glycogen storage in the liver<sup>18</sup> and abolish hypoglycemia in adrenalectomized animals and in Addison's disease, and increase glycconeogenesis from body proteins. Desoxycorticosterone acetate has no direct effect on carbohydrate metabolism.

Because of these many physiologic functions that are directly or indirectly the responsibility of healthy adrenals, it is well to consider the possibility of hypofunction of the adrenals when dealing with unexplained, protracted illnesses of premature and young infants, especially those illnesses associated with anorexia, vomiting, loose stools, persistent tendency to dehydration, hypoglycemia, and failure to gain weight, after adequate nursing and medical procedures have failed to restore the infant to normalcy.

The following cases present a variety of symptoms ranging from attacks of hypoglycemia, anorexia, listlessness, and failure to gain weight, to unexplained, protracted diarrhea. The "present illness" in every patient began in the neonatal period. A brief summary and discussion precede each case report.

*Summary, Case 1.*—J. W., a newborn male, presented an unusual picture of severe hypoglycemia associated with pronounced and prolonged tendency to dehydration without diarrhea or vomiting. The hypoglycemia did not readily respond to the administration of subcutaneous or oral glucose. The rise of the blood sugar from 16.0 mg. per cent to 183 mg. per cent after administration of adrenalin is evidence that the hypoglycemia was not on the basis of depleted liver glycogen. A combination of pork adrenal cortex extract\* and desoxycorti-

\*"Pork adrenal cortex extract" contains 40 rat units per cubic centimeter. Each cubic centimeter contains 10 mg. of 17-hydroxy-11-dehydrocorticosterone (compound E) or 4 mg. of extract is put up in oil. It was supplied through the courtesy of Upjohn Company, Kalamazoo, Michigan.

costerone acetate adequately controlled the hypoglycemia and restored the electrolyte and water balance which was previously uncontrolled. The low serum sodium chloride of 66.7 milliequivalents per liter, obtained after frequent administration of normal saline subcutaneously, is presented as further evidence of a low adrenal cortical function.

The cerebral manifestations with subsequent mental retardation may possibly be due to the severe, prolonged hypoglycemia and associated anoxia during the early days of life.

CASE 1.—J. W., a two-day-old male infant, was admitted to St. Louis Children's Hospital Dec. 5, 1944. Birth weight was 2,800 Gm. In the forty-eight hours immediately following spontaneous delivery he was apparently normal. Periods of apnea and cyanosis then developed, which were relieved by carbon-dioxide inhalations, but the baby remained limp and unresponsive. C. W. B. T. glucose\* was 5.0 mg. per cent. Spinal fluid was crystal clear but slightly xanthochromic. The skin was moderately jaundiced. The patient was given 10 per cent glucose intravenously and 5 per cent glucose in normal saline subcutaneously. Five hours later, twitchings of all extremities and irregular respirations occurred. Heart and lungs were negative, and blood pressure was 54 systolic. C. W. B. T. glucose later that day was still only 5.0 mg. per cent, despite intravenous and subcutaneous glucose. The patient was placed in an oxygen tent, 5 per cent glucose in normal saline was kept in the tissues constantly, and 10 per cent glucose offered by mouth every three hours. Twenty-four hours after the therapy, C. W. B. T. glucose was only 8.0 mg. per cent. One cubic centimeter of whole beef extract† was given immediately and 0.2 c.c. was given every four hours. On Dec. 9, 1944, C. W. B. T. glucose was 16 mg. per cent; 3 minims of adrenalin were given, and twenty minutes later C. W. B. T. was 183 mg. per cent. Periods of cyanosis became less marked, but occasional twitchings continued. Muscular tone improved, but marked tendency to diuresis developed. On December 11, true serum glucose was 5.0 mg. per cent; carbon-dioxide combining power was 58.5 volumes per cent; icterus, 28; nonprotein nitrogen 20 mg. per cent; total serum protein, 5.13 Gm.; serum calcium, 12.1 mg. per cent; serum phosphorus, 6.5 mg. per cent; total serum sodium chloride, 66.7 milliequivalents per liter. Urine was large in volume; specific gravity, 1.006; albumin, negative. Rothera, ferric chloride microscopic, and sugar tests were negative. Glucose was administered twice daily intravenously and subcutaneously. While the patient remained on whole beef extract every four hours there were fewer episodes of cyanosis and twitching, and blood sugars remained between 20 and 39 mg. per cent. When extract was withheld there was an increase in attacks of cyanosis and twitching, and associated lowering of blood sugar to between 5 and 15 mg. per cent. From Dec. 14 to Dec. 21, 1944, the infant's condition remained the same. The child was not gaining weight despite excessive amounts of subcutaneous and intravenous fluids. On December 19, daily injection of 1.0 mg. desoxycorticosterone acetate and 0.25 c.c. pork adrenal cortex extract‡ was begun. Immediately following this therapy, all twitching and cyanosis ceased. The patient was much less listless, blood sugars were maintained between 40 and 50 mg. per cent, and hydration was easily maintained without usual parenteral fluids. The total serum chloride rose to 106.1 milliequivalents per liter, and nonprotein nitrogen to 25 mg. per cent. When hormone therapy was stopped, blood sugar ranged between 10 and 20 mg. per cent and severe dehydration was evident.

When 1.0 mg. desoxycorticosterone acetate and 0.25 c.c. of pork adrenal cortex extract were resumed, the patient began to act and look like a normal infant, blood sugar became

\*C.W.B.T. Capillary whole blood "true" glucose. This method utilizes the zinc sulphate—sodium hydroxide precipitating reagents of Somogyi and the sensitive Shaffer-Somogyi low blank reagent.

†Whole beef extract or adrenal cortex extract. Each cubic centimeter is obtained from not less than 40 Gm. of adrenal gland and contains not less than 50 dog units or 2.5 rat units. This extract is water soluble. It was supplied by the Upjohn Company.

elevated to normal, and hydration was restored. Starting Jan. 26, 1945, the adrenal hormones were gradually discontinued and blood sugars maintained between 65 and 70 mg. per cent. Weight on discharge was 3,800 Gm.

The patient was readmitted to the hospital at 7 months of age because of frequent transient episodes of generalized clonic convulsions of one month's duration. The child was mentally retarded, and could not hold his head erect or sit alone. Nonprotein nitrogen was 29.0 mg. per cent; carbon-dioxide combining power, 38 volumes per cent; total protein, 6.75 Gm.; sodium chloride, 93.1 milliequivalent<sup>s</sup> per liter; blood sugar, 57.0 mg. per cent. On July 20, 1945, oral glucose tolerance and, on July 24, insulin tolerance were essentially normal.

*Summary, Case 2.*—L. P. presented a common and serious problem of protracted diarrhea beginning in the early days of life. Periods of acidosis and dehydration were frequent. An attack of several hypoglycemia was encountered, nearly resulting in death of the patient. After one month of accepted treatment without appreciable change in the condition, whole cortical extract was administered, which resulted in rapid improvement in the appearance of the baby and disappearance of diarrhea. After whole beef extract was stopped there was rapid loss of weight, but no reappearance of diarrhea. Hydration was immediately restored following desoxycorticosterone acetate administration. Pork adrenal cortex extract may have favorably influenced the blood sugar levels; however, one cannot be certain because of the short duration of the hypoglycemia. Unfortunately, blood electrolyte determinations were not done.

CASE 2.—L. P., a full term, female, was born by spontaneous delivery Aug. 17, 1945. Birth weight was 3,800 Gm. She was well until the ninth day of life, when frequent watery stools and occasional vomiting began. Despite adequate parenteral therapy for a period of two weeks in a neighboring hospital, there was a steady decline and she was transferred to St. Louis Children's Hospital on September 25, at 6 weeks of age. The patient weighed 2,580 Gm., was markedly emaciated, dehydrated, very weak, and listless. There was no evidence of parenteral infection. Hemoglobin was 11.0 Gm., white blood cell count was 8,100 with normal differential. Carbon-dioxide combining power was 32.5 volumes per cent; and blood culture was sterile. Stool cultures showed a slow lactose fermenter of the colon group. The patient was given routine molar lactate therapy, and placed on one-third diluted, skimmed, evaporated milk. On October 24, after one month's hospitalization with no appreciable improvement, the infant suddenly became apneic and gray, and was in a state of collapse. C. W. B. T. glucose during this episode was 6.0 mg. per cent. Five minims of adrenalin were given subcutaneously and in one-half hour the C. W. B. T. glucose was 65.0 mg. per cent, and the patient was much improved. Daily injection of 2.0 c.c. whole beef adrenal cortical extract was begun. Single urine specimens contained large amounts of chlorides. Two days following therapy there was obvious improvement in stools; the patient was stronger, more alert, took food better, and began to gain weight without parenteral fluids. Urine contained only traces of chlorides when diarrhea subsided. When the adrenal hormone therapy was begun, weight was 2,560 Gm.; four days later it was 2,960 Gm. Five days after therapy, diarrhea had completely disappeared for the first time since the age of 9 days. On October 31, C. W. B. T. glucose was 71.0 mg. per cent. On October 28, whole beef extract was discontinued, and 0.25 c.c. pork adrenal cortex extract given intramuscularly every other day. Nonprotein nitrogen was 41.0 mg. per cent, and carbon-dioxide combining power 50 volumes per cent on October 30. After change to pork adrenal extract, blood sugar remained normal and diarrhea did not reappear, but there was a rapid weight loss to 2,560 Gm. by October 31. December 1, daily injections of 2.0 mg. desoxycorticosterone acetate were begun. Three days later weight had risen to 2,820 Gm. without visible evidence of edema. Desoxycorticosterone acetate was discontinued on December 12, and the patient was

discharged December 24 weighing 2,800 Gm. Caloric intake was then gradually increased without recurrence of diarrhea, and on Jan. 3, 1946, weight was 4,000 Gm. When last seen, at 9 months of age, the child was found to be perfectly normal.

*Summary, Case 3.*—L. Y., a female premature infant, developed anorexia, steady weight loss, and frequent periods of dehydration despite adequate parenteral therapy. No gastrointestinal disturbances were noted. An attack of hypoglycemia was immediately relieved by intravenous glucose. After administration of pork adrenal cortex extract and desoxycorticosterone acetate, prompt clinical improvement was evidenced, hydration was restored, and clinical manifestations of hypoglycemia did not reappear. Death was caused by aspiration of milk. Post-mortem examination was denied.

CASE 3.—L. Y., a two months premature, female infant was born Dec. 8, 1944. Birth weight was 1,600 Gm. There was an uncomplicated delivery, spontaneous cry, and normal birth. She was admitted to St. Louis Children's Hospital at 13 days of age because of gradual weight loss and anorexia. There was no history of diarrhea or vomiting. The patient was listless, dehydrated, and weighed 1,180 Gm. Temperature was 34.6° C.; Hemoglobin, 11.2 Gm.; red blood cell count, 3.71 million; white blood cell count, 17,250; normal differential count. Kahn test was negative. The infant was given routine premature care and penicillin, 5,000 units every three hours. She was much improved shortly after entry, but twenty-four hours later was found to be cyanotic, apneic, and in state of collapse. C. W. B. T. glucose was 10.0 mg. per cent; after intravenous injection of 10 per cent glucose, and 5 per cent glucose in normal saline subcutaneously, active cry and normal color returned. Following this episode, 2.0 mg. desoxycorticosterone acetate and 0.25 c.c. of pork adrenal cortex extract were administered intramuscularly. Twenty-four hours later the patient was much better hydrated, more active, and appeared to be well on the way to recovery. The pork adrenal cortex extract and 0.5 mg. desoxycorticosterone acetate were administered again the following day. Two days after onset of therapy the weight was 1,310 Gms. The next day the patient vomited, aspirated milk, and choked to death. No post-mortem examination was obtained.

*Summary, Case 4.*—M. G., a premature infant, developed a staphylococcus septicemia and urinary infection during the course of a severe diarrhea. The sepsis was readily controlled by the use of penicillin and sulfadiazine. Following the eradication of the infection, periods of unexplained dehydration and attacks of hypoglycemia developed. These episodes were associated with collapse and extreme listlessness. After two days of adrenal hormone therapy, there was no return of the hypoglycemia; marked improvement in the diarrhea was noted, resulting in an increased appetite, better hydration, and a more vigorous baby. It was felt that the diarrhea and the transient sepsis probably added greatly to the demands made on the physiologically low functioning adrenal cortex. These demands could not be promptly met, and because of probable poor intestinal absorption of glucose, possible lack of liver glycogen or poor mobilization, hypoglycemia resulted. Administering adrenal steroids was seemingly sufficient to meet the increased need for circulating hormones and tide the infant over this critical period.

CASE 4.—M. G., a female twin, was born by spontaneous delivery, three weeks premature. on Dec. 5, 1944, with a birth weight of 2,320 Gm. On the fourth day of life watery stools developed, followed by a rapid loss of weight despite adequate parenteral therapy. When

seven days old, she was admitted to St. Louis Children's Hospital, weighing 2,070 Gm. Both eardrums were slightly thickened and the skin was dehydrated but the infant was fairly alert and hungry. The carbon-dioxide combining power was 37 volumes per cent; blood and stool cultures were negative. Kahn and tuberculin tests were negative. Usual amounts of parenteral fluids and sulfadiazine therapy were begun, and the next few days there was some improvement in the diarrhea. December 29 diarrhea suddenly became worse; vomiting commenced, and periods of unexplained listlessness and collapse followed. Blood culture grew out a few colonies of *Staphylococcus aureus*, and growth of *Bacillus coli* was cultured from the urine, although the blood sulfadiazine level was 8.9 mg. per cent. Penicillin, 5,000 units every three hours, was administered, and subsequent blood cultures were sterile. Despite improvement in the diarrhea and disappearance of parenteral infection, periods of collapse, extreme listlessness, and dehydration continued. On January 3, the spinal fluid was found to be crystal clear, Pandy reaction negative, 3 cells. The spinal fluid glucose was 10.0 mg. per cent, C. W. B. T. glucose taken the same day about two hours after feeding was 29.0 mg. per cent. January 5, the C. W. B. T. glucose was 10.0 mg. per cent, and 2 minims of adrenalin were given subcutaneously between feedings for twenty-four hours. The following day, daily injections of 0.25 c.c. pork adrenal cortex extract and 0.5 mg. desoxycorticosterone acetate were instituted. In next two days there was little change, and C. W. B. T. glucose ranged from 5.0 mg. per cent to 25.0 mg. per cent. By January 9, there was a decided improvement. The patient became more alert and eager to feed, and no further periods of listlessness, dehydration, or collapse were noted. The blood sugar ranged from 40 to 77 mg. per cent. The blood pressure rose from 70/40 systolic to 98/60. The pork adrenal extract and desoxycorticosterone acetate were gradually discontinued without recurrence of symptoms. The infant was discharged January 25, weighing 2,340 Gm. Growth and development have been normal.

*Summary, Case 5.*—The illness of K. S., a female premature infant, began with frequent attacks of convulsions the first few days of life, followed by a failure to gain weight. At first, response was favorable to routine premature care, but she later developed anorexia, moderate number of loose stools, and a pronounced tendency to dehydration. *Staphylococcus septicemia* developed, and later a localized abscess of the back was incised. The infection promptly responded to penicillin therapy, but loose stools continued, and the patient appeared to be slowly dying. After administration of desoxycorticosterone acetate there was a rapid improvement in hydration, disappearance of the diarrhea, and return of pink color and normal activity. She has subsequently remained well.

*CASE 5.*—K. S., a female, premature infant, one of identical twins, was born Aug. 31, 1944, after normal delivery. Birth weight was 1,820 Gm. She had a history of cyanosis at birth and frequent attacks of generalized twitchings the first few days. She was admitted to St. Louis Children's Hospital on September 9 because of failure to gain weight. Weight was 1,500 Gm. She was active, had good color and no evidence of infection. Physical examination was essentially negative. The infant did well on the usual premature routine, and by September 27, her weight had increased to 2,320 Gm. Then there was a gradual loss of appetite, occurrence of loose stools, and weight decrease to 1,860 Gm. by October 4. She began to vomit all feedings. The usual therapy of parenteral fluids, intravenous glucose, blood transfusion, vitamins, and sulfadiazine was given. On October 5, blood culture grew out *Staph. aureus*. Urine was clear. Four days later a localized abscess of back was found, incised, and drained. Pus from the abscess also cultured out *Staph. aureus*. Penicillin in addition to sulfadiazine was given, and a few days later the back had completely healed, and blood cultures became sterile. Despite the eradication of all known infection, the patient showed little improvement, requiring frequent subcutaneous fluids to maintain hydration; the stools continued to be loose but not frequent. On November 4, the assistant Resident noted: "The baby looks as though it is dying of old age." Skin was atrophic,



dehydrated, and slightly icteric. On November 5, 2.0 mg. desoxycorticosterone acetate were given. Twenty-four hours later the baby looked better; color and appetite improved. Desoxycorticosterone acetate, 0.5 mg., was given daily. On November 7, the infant began to cry hungrily between feedings, and stools were more formed. On November 4, the weight was 1,880 Gm. and by November 10, it had risen to 2,240 Gm., without parenteral fluids. Desoxycorticosterone acetate was continued through November 20, and then gradually stopped. The patient was discharged December 5, weighing 2,760 Gm. Reports from the mother indicate normal growth and development at 9 months of age.

*Summary, Case 6.*—A. S., identical twin of Case 5, presented a similar history. She also developed loose stools and was very difficult to keep hydrated. The patient's condition differed from that of her twin in two respects only; first, there was no definite evidence of infection; secondly, hypoglycemia symptoms developed. This infant did not receive desoxycorticosterone acetate; otherwise, the treatment was identical in the two cases. Post-mortem examination showed very little other than a small patch of terminal bronchopneumonia. The slight cirrhosis of the liver may have been a factor in the development of the hypoglycemia. The endocrine organs were said to have been normal for a premature infant.

CASE 6.—A. S., was a female, identical twin, whose sister was admitted to the hospital at the same time. Born Aug. 31, 1944, her birth weight was 2,200 Gm. She had a history of cyanotic attacks and generalized twitchings the first few days. She entered St. Louis Children's Hospital Sept. 9, 1944, because of failure to gain weight. Her weight was 1,350 Gm. The infant was weak and listless, but had good color and physical examination revealed no abnormalities. There was no evidence of infection. Kahn test was negative. She was given identical premature care to that of her twin. By September 29, her weight had increased to 1,650 Gm. From this time on, a few loose stools were noted, and weight dropped to 1,560 Gm. within a few days. Her skin became slightly icteric, turgor poor, and she became dehydrated and listless. Frequent administration of subcutaneous fluids and blood transfusions were necessary. October 20, the infant became stiff and pale. Blood calcium was 12.5 mg. per cent, and nonprotein nitrogen, 28 mg. per cent. Following intravenous glucose, there was definite improvement. The serum glucose was 15.0 mg. per cent. On October 27, there was definite jaundice evident, and icterus index was 61.0 mg. per cent. Nonprotein nitrogen was 29.0 mg. per cent; total proteins, 5.5 gm.; and serum glucose, 17.0 mg. per cent. Blood cultures were sterile. Sulfadiazine and penicillin therapy were begun. On Oct. 30, 1944, the carbon-dioxide combining power was 31.6 volumes per cent, serum glucose, 54.0 per cent, and non-protein nitrogen, 29.0 mg. per cent. Loose stools continued and hydration was very difficult to maintain. By November 2 she was less jaundiced. Icterus index was 20 mg. per cent, but the baby remained weak, took formula poorly, and would dehydrate rapidly despite frequent administration of fluids. On November 3, her respiration was shallow and color gray. Intravenous glucose resulted in immediate crying and improvement in color, and the patient remained improved until three hours later when she was found gasping and failed to respond to emergency measures. She expired November 3. Necropsy revealed slight cirrhosis of the liver and slight generalized icterus of all organs. The only evidence of infection was a small patch of terminal bronchopneumonia. All other organs of the body were normal for a premature infant.

*Summary, Case 7.*—B. S., a full-term infant, had a severe physiologic icterus and later developed protracted diarrhea associated with periods of acidosis and a marked tendency to dehydration, despite frequent administration of parenteral fluids. Three weeks after entering the hospital the baby was emaciated and

listless, and there was no significant improvement in diarrhea. Improvement in hydration, number of stools, and general well-being of the infant was noted following the administration of desoxycorticosterone acetate. Here again, it is felt that supplying the cortical steroid during this critical period was sufficient to take care of extra demands that could not be met by the patient's adrenal glands.

CASE 7.—B. S., a full-term female infant, was born May 11, 1945, with spontaneous cry and respiration. Birth weight was 2,900 Gm. The patient was reported slightly jaundiced at birth. Progressive increase in icterus was noticed. Mother, father, and baby were all found to be Rh positive. The infant was admitted to the St. Louis Children's Hospital June 13, 1945, with a weight of 2,800 Gm. The child was active, well developed, and nourished. Skin and sclerae were very jaundiced. Kahn test was negative; hemoglobin, 17.4 Gm.; red blood cell count, 4.5 million; urine, negative. By June 17 the icterus was diminishing. The course was uneventful until June 21, when vomiting and loose stools developed, resulting in a marked weight loss. Routine parenteral therapy, plus penicillin, 5,000 units every two hours, was begun. There was no evidence of infection. The diarrhea persisted with frequent periods of acidosis. June 23, the C. W. B. T. was 105 mg. per cent. Large amounts of parenteral fluids and intravenous glucose were required to maintain hydration. July 4, three weeks after entry, her weight was 2,340 Gm. and there was no significant improvement. An initial dose of 2.0 mg. desoxycorticosterone acetate was given, then 0.5 mg. daily for the following three days. Prompt hydration and general improvement in the color, appetite, and activity were noted. By July 7, stools were much improved; serum sodium chloride was 120.0 milliequivalents per liter, glucose was 61.5 mg. per cent, and nonprotein nitrogen, 27.6 mg. per cent. Weight rapidly increased from 2,340 Gm. to 2,580 Gm. four days later, and parenteral fluids were no longer required. The patient continued to improve after desoxycorticosterone acetate was discontinued. She was discharged July 14 weighing 2,760 Gm. The child has remained well.

*Summary, Case 8.*—G. T., a male infant, entered the hospital at 3 weeks of age because of failure to gain weight. There was a history of convulsions during the early days of life. A urinary infection was found, which readily cleared after penicillin and chemotherapy. After three weeks of constant care, the appetite remained poor, and the infant continued to be listless. Hydration was maintained only by daily administration of parenteral fluids. These symptoms, plus a moderately low serum sodium chloride, elevated nonprotein nitrogen, absence of free hydrochloric acid of the stomach, and a peculiar "dirty" pigmentation of the skin, suggested possible hypofunction of the adrenal cortex. The rapid improvement following desoxycorticosterone acetate therapy strengthened this impression. It is of interest to note that the patient got along well at home for one month on the addition of table salt to the formula, but later required desoxycorticosterone acetate again. Before therapy was started, it was found that the sodium was low and potassium definitely elevated. Following desoxycorticosterone acetate therapy, the sodium and potassium levels returned to normal, and the patient progressed normally.

The determination of urinary steroids ruled out the possibility of an androgenic hyperplasia associated with hypofunction of the "true" cortex.<sup>3</sup> There has been no evidence suggesting adrenal tumor, although pyelograms have not been done. This is the first and only case in this series requiring prolonged hormone therapy. The patient at present requires daily injections of de-

soxycorticosterone acetate; therefore, one cannot be certain whether or not this is a case of physiologic low activity of the adrenal cortex. In experimental animals, the prolonged administration of cortical hormones may lead to atrophy of the adrenal gland. This possibility must also be considered, provided it remains necessary to continue the injections of desoxycorticosterone acetate.

CASE 8.—G. T., a three-week-old male, was born April 12, 1945, after a normal, uncomplicated delivery. Birth weight was 3,180 Gm. The baby appeared normal after birth with the exception of underdeveloped genitalia; the testes were undescended, and there was a hypospadias. On the second day of life, generalized convulsions, periods of apnea, and cyanosis developed. Following this, the infant lost weight steadily and appetite remained poor. Urinalysis one week before admission showed many pus cells, albumin, and bacteria. Stools were normal and there was no vomiting. He entered St. Louis Children's Hospital May 3 because of weight loss. A small, thin, malnourished infant, he weighed 2,660 Gm. Physical examination was essentially negative with the exception of the penis, which was small and hung as if bound down to undeveloped scrotum. Urine contained 50 to 60 pus cells per low power field, one plus albumin, *Bacillus coli* and few staphylococci. Penicillin and sulfanilamide were started, and in a few days the urine was completely cleared. On May 4, nonprotein nitrogen was 49.5 mg. per cent, carbon-dioxide combining power was 60.8 volumes per cent, calcium, 11.8 mg. per cent, phosphorus 7.4 mg. per cent, blood culture, sterile. May 24, three weeks later, there had been no weight gain; the patient was listless and nursed poorly. Daily parenteral fluids were required to prevent dehydration. There was no evidence of infection since the transient pyuria. On May 30, when first seen through the courtesy of Dr. J. V. Cooke, the patient appeared chronically ill. There was a peculiar "dirty gray" pigmentation of the skin. Blood pressure was 80 systolic, which is low for the cuff used. Nonprotein nitrogen was 59.0 mg. per cent, carbon-dioxide combining power was 57 volumes per cent, and total serum sodium chloride, 86.7 milliequivalents per liter. Gastric analysis showed no free hydrochloric acid. C. W. B. T. glucose was between 77 mg. per cent and 84 mg. per cent. On May 31, 1945, daily doses of 1.0 mg. desoxycorticosterone acetate were started. Three days later, the patient was obviously more active and his appetite improved. Weight before hormone therapy was 2,625 Gm. An average of 250 c.c. of subcutaneous fluids was required daily to prevent weight loss. June 11, after 1.0 mg. desoxycorticosterone acetate had been given for eleven days, no parenteral fluids were required, and there was a steady gain in weight to 2,855 Gm. Desoxycorticosterone acetate was discontinued June 11. The patient continued to improve and was discharged July 3 weighing 3,100 Gm. The mother was instructed to put 3.0 Gm. of table salt in the total day's formula. Seen again August 16, weight was 4,800 Gm., but the "dirty gray" skin color was still present. Blood pressure was 94/60; serum sodium chloride, 97.5 milliequivalents per liter; nonprotein nitrogen, 37.5 mg. per cent. Urine was clear and strongly positive for chlorides. On Aug. 21, 1945, the patient was readmitted to the hospital because of sudden onset of anorexia, vomiting, and loose stools of two days' duration. His weight was 4,540 Gm., he was irritable, listless, and moderately dehydrated. There was no evidence of infection. The patient was given parenteral fluids and started on formula with 3.0 Gm. table salt added. Aug. 24, 1945, serum glucose was 78 mg. per cent; nonprotein nitrogen, 35.5 mg. per cent; carbon-dioxide combining power, 43.5 volumes per cent; and serum sodium chloride, 88.6 milliequivalents per liter. The patient ate poorly and required frequent administration of subcutaneous fluid, despite cessation of vomiting and diarrhea. September 3 while on 3.0 Gm. of table salt in formula, the total serum sodium chloride was 98.4 milliequivalents per liter; sodium, 130.9 milliequivalents per liter; and potassium, 10.2 milliequivalents per liter. September 4, weight was 4,330 Gm. The next day, desoxycorticosterone acetate was begun and parenteral fluids discontinued. A dose of desoxycorticosterone acetate varied from 1.0 to 2.0 mg. There was a gradual increase in weight, and by Sept. 27, 1945, when the steroid was discontinued, the weight was 4,925 Gm. The patient continued to look well, but there was a slow, steady loss

of weight. On October 6, daily doses of 5.0 mg. desoxycorticosterone acetate were begun. The patient was discharged three days later. Urine was collected for steroid determination. Dr. Willard Allen's note read: "The total urinary steroids and the 17 ketosteroids are both below 1.0 mg. per day. This indicates that there is no adrenal hyperfunction insofar as the androgens are concerned." The patient was seen again November 4. During this interval he received daily injections of 5.0 mg. desoxycorticosterone acetate and 3.0 Gm. sodium chloride in each day's formula. Weight was 7,020 Gm., and there was no evidence of edema. The patient was normal in every respect. Blood pressure was 92/60; heart, normal; serum sodium chloride, 104.4 milliequivalents per liter; sodium, 143.1 milliequivalents per liter; potassium, 6.9 milliequivalents per liter. Desoxycorticosterone acetate was then given every other day and by Jan. 3, 1946, his weight was 7,900 Gm., with the skin pigmentation barely noticeable. Desoxycorticosterone acetate was discontinued entirely. Immediate failure of appetite and rapid weight loss ensued. The patient still requires 2.0 to 3.0 mg. desoxycorticosterone acetate daily, but an attempt is being made to gradually reduce the dosage.

*Summary, Case 9.*—S. D., a full-term male, developed disturbance of gastrointestinal function in the early days of life. The repeated bouts of diarrhea, vomiting, and inability to gain weight remained essentially unaltered, despite everything that could be done over a period of two and one-half months' hospitalization. Within a short period following administration of adrenal cortex extract, the stools became normal, and appetite increased. Despite the development of an extensive virus pneumonitis, the diarrhea did not recur while the patient was on extract. There was no appreciable gain in weight until desoxycorticosterone acetate was given daily. A most interesting finding was that of low trypsin activity before prolonged hormone therapy and a return to normal after treatment. The skin discoloration was very similar to that of the patient in Case 7.

CASE 9.—S. D., a full-term male, was born June 29, 1945, by spontaneous delivery, and was apparently normal except for loose stools, averaging eight or nine per day. During the first three weeks of life there were frequent periods of vomiting, and just before entering the hospital, stools became more frequent. The patient was admitted to the hospital August 18. He was gray, markedly dehydrated, and very listless; the fontanelle was sunken and the heart was small. Genitalia were normal. There was no evidence of parenteral infection. Urine was clear and alkaline in reaction. Nonprotein nitrogen was 62 mg. per cent, blood culture, sterile. The infant was given 10 per cent glucose intravenously, fortified lactate Ringer's subcutaneously, blood transfusions, and parenteral vitamins. On August 20, carbon dioxide was 64.4 volumes per cent. Two months later there was little change in the patient's condition. October 23, Dr. A. F. Hartmann's note read: "Patient began to vomit in early infancy, then developed diarrhea and has continued to have diarrhea with but short periods of remission." On October 29, carbon dioxide was 62 volumes per cent; nonprotein nitrogen, 41.0 mg. per cent; and serum glucose, 60.1 mg. per cent. The patient gradually lost ground. Weight was 2,840 Gm., only 40 Gm. above that on admission two and one-half months previously. Skin was a "dirty gray" in appearance. October 29, when I first saw the patient through the courtesy of Dr. Hartmann, daily injections of 5.0 c.c. of whole beef adrenal extract were begun. The following day the patient was fairly alert and cried for food, and oxygen tent was no longer required. He was kept on food by mouth despite loose stools. Five days after adrenal hormone therapy, stools were almost normal, appetite decidedly increased, and weight increased to 4,020 Gm. without the large amounts of parenteral fluids formerly required to maintain hydration. Thirteen days after hormone therapy, on Nov. 15, 1945, there had been ten days of normal to constipated stools, with no parenteral fluids necessary and an appetite which improved

radily. November 16, there was sudden elevation of temperature, weight loss to 3,460 Gm. and skin dehydration, but no vomiting or return of diarrhea. Urine samples contained large amounts of chlorides. The fluoroscopic examination showed extensive infiltration in the right lung. White blood cell count was 4,980; stab cells, 4; segmented cells, 18; lymphocytes, 5; and monocytes, 11. A diagnosis of atypical pneumonia was made. Penicillin, 5,000 units every three hours, was started. The temperature subsided rapidly. Because of pronounced tendency to dehydration with onset of infection, the whole adrenal gland extract was discontinued, and a daily dose of 5.0 mg. desoxycorticosterone acetate was started. Within six days weight increased from 3,400 Gm. to 4,300 Gm., and appetite returned to normal. By November 21, desoxycorticosterone acetate was administered every other day and weight dropped to 3,750 Gm. On November 29, daily doses of desoxycorticosterone acetate were resumed, resulting in a steady weight gain and general improvement and on December 8, weight was 4,520 Gm. Six days later desoxycorticosterone acetate was discontinued and the patient remained well. December 5, the serum sodium chloride was 8 milliequivalents per liter. The patient was discharged Dec. 19, 1945, weighing 4,880 Gm.

On November 8, Dr. Gilbert Forbes had examined the duodenal juice for "trypsin activity" and found a marked decrease. December 17, after desoxycorticosterone acetate therapy, this examination was repeated, and normal tryptic activity was found. The patient continued to do well and on Jan. 23, 1946, weighed 6,590 Gm.

#### DISCUSSION AND SUMMARY

There has been relatively little investigation of the activity of the adrenal cortex during the early days of life. Bruch and McCune<sup>19</sup> made a biochemical investigation into the physiologic significance of involution of the adrenal glands in newborn infants. They could not demonstrate blood chemical changes similar to those seen in Addison's disease.

Miller<sup>20</sup> demonstrated that the blood sodium level rose after the first few days of life. He states that the low values may be interpreted as either evidence of shock or adrenal insufficiency. He also showed that the physiologic weight loss, which averages 6.5 to 7.8 per cent in newborns, was reduced to an average of 4.5 per cent after the administration of desoxycorticosterone acetate. Miller suggests that adrenocortical insufficiency may be another factor producing the physiologic weight loss.

Collis<sup>21</sup> in his paper, "Premature Infant's Management and Prognosis," wrote a brief paragraph recommending adrenal extract for relief of dehydration with ketosis in premature infants. No further statement was made. On the other hand, Young and associates<sup>22</sup> in their investigation of renal function of premature infants, suggested that a low glomerular filtration rate combined with an overactive suprarenal cortex might account for the very low mineral clearances. They were, however, unable to explain the low potassium clearances on this basis. Akerren<sup>23</sup> in his excellent paper, "Shock in Premature Children," states that Cortin has had a favorable effect on the debilitated infant. No details were presented.

The use of biochemical changes alone to rule out hypofunction of the adrenal cortex has its limitations, particularly when we realize that infants have much lower renal mineral clearances the first few weeks of life than at any other time.<sup>22</sup> The electrolyte picture of the blood may be perfectly normal in some cases of Addison's disease and in adrenalectomized animals. The flooding of the

fetus with estrogenic hormones from the placenta, plus the low renal mineral clearance of the newborn and premature infant may be the reason why it has been difficult to demonstrate blood chemical changes suggesting hypofunction of the adrenal cortex.

During most of the intrauterine period the true cortex remains as a thin rim of closely packed cells with deeply stained nuclei. The X zone, fetal cortex, or androgenic zone, comprises the largest part of the adrenal gland, and grows rapidly during the intrauterine period. It seems likely that because of the unusually small amount of the true cortical tissue, the fetus does not rely entirely on the secretions of hormones from this tissue for its rapid growth and development. Immediately following birth, the androgenic tissue involutes, and there is most likely an increased need for secretion of hormones from the true cortex. This demand increases from day to day, and, as a result, there is a corresponding enlargement in size of this tissue during the first four weeks.<sup>24, 25</sup> During this adjustment period could not there be a physiologically low activity of the true cortex? This concept, if true, could explain the reason for many deaths in premature and full-term infants the first few weeks of life, which are preceded by periods of unexplained and prolonged debility not responding to treatment. It would also answer a question which has puzzled physicians for many years, namely, why do certain infants fail to recover following various diseases contracted during early life, despite the complete eradication of the infection? The most recent investigations<sup>1, 26, 27</sup> have shown that there is a physiologic hypoglycemia during the first few days of life which may be explained by a lack of adrenal cortical or anterior pituitary secretions, physiologic hyperinsulinism, immature liver, or a combination of these. The hypoglycemia might be interpreted as a disturbance in carbohydrate metabolism secondary to low adrenal function. The rapidity with which glycogen disappears in the newborn liver after fasting is also suggestive of low cortical function. Rushton and associates<sup>28</sup> reported a case of an adult who had severe attacks of hypoglycemia without signs or symptoms of Addison's disease. Post-mortem examination revealed the adrenal glands to be markedly atrophic.

Himwich<sup>29</sup> has shown that in newborn infants and young animals the cerebral metabolism is very low. He and others have emphasized that the foremost antagonist to the parasympathetic-insulin apparatus is the sympathetic adrenal system which is "probably functioning poorly or not at all in the newborn the first few days of life." Adrenalin has been demonstrated in the adrenal medulla of animal fetuses, however "the human fetal medulla seems almost without its presence."<sup>30</sup> Recently Vogt<sup>31</sup> in investigating various conditions affecting the rate of hormone output by the suprarenal cortex, demonstrated that through adrenalin the sympathetic nervous system has an indirect control over the activity of the adrenal cortex. If the sympathetic adrenal system is functioning poorly in newborns the first few days of life, even though there were small amounts of the cortical hormone present, it may not be available when most needed.

Each of the cases reported here may present some phase of hypofunction of the adrenals. The patients treated were those which showed little hope of recovery, and any therapeutic measures which had the slightest chance of benefiting the patient were justified, no matter how drastic. It is difficult to portray the critical state of these patients and the dramatic improvement following hormone therapy.

With the exception of Cases 2 and 3, the patients were observed for from three to ten weeks in the hospital, with no demonstrable improvement in their conditions before hormone therapy was started.

The characteristics common to every infant described here are: general debility and weakness, appearance of impending shock, and marked tendency to dehydration, in spite of adequate parenteral fluid therapy. In addition to these signs, five of the nine patients (Cases 1, 2, 3, 4, and 6) had superimposed attacks of hypoglycemia that were immediately relieved by elevation of the blood sugars. Although it is well known that blood sugars may be extremely low in surviving premature infants,<sup>32</sup> the symptoms of collapse associated with low blood sugars, the immediate improvement after intravenous glucose, and the failure of return of these symptoms during periods of elevated blood sugar levels would be difficult to explain on the basis of physiologic hypoglycemia.

Two patients (Cases 1 and 3) had no evidence of infection or gastrointestinal disturbances. Four patients (Cases 2, 6, 7, and 9) had anorexia and loose stools from the early days of life without evidence of infection. One patient (Case 8) had a transient urinary infection without gastrointestinal disturbances other than anorexia. Two patients (Cases 4 and 5) with diarrhea developed staphylococcus septicemia readily responding to penicillin, but loose stools continued, and downhill course persisted until hormone therapy was started.

In addition to the cases listed above, over a period of three years at least a dozen premature infants have been observed who have shown prompt and beneficial response to the administration of whole adrenal extract (Upjohn's "adrenal cortex extract") in dosage of 1.0 c.c. per kilo body weight per day, given subcutaneously. Almost without exception improvement was noted within two to three days of the injection and was indicated by increased appetite, maintenance of hydration without parenteral fluids, and a more vigorous baby. The therapy was continued on the average of seven days and then stopped with no discernible relapses.

The daily dosage of desoxycorticosterone acetate varied from 0.5 to 5.0 mg., depending upon the clinical response. These are relatively large doses of adrenal steroids, compared to those required in the regulation of Addison's disease in adults. The tissues of early infancy may fail to completely absorb the oil, and it is sometimes difficult to be certain all of the injection is given into the muscle. Another explanation for the necessity for large doses is the possibility that this is not a replacement therapy after all, but rather a nonspecific action of the steroids. Possibly, if regulated amounts of electrolytes are given by mouth the effective doses of desoxycorticosterone acetate may be lowered.

Although no harmful effects have been noted from the administration of the adrenal hormones, with the possible exception of Case 8, a warning should be given against the promiscuous use of desoxycorticosterone acetate. Experimental and clinical observations<sup>13, 34</sup> have definitely shown that when excessive doses of desoxycorticosterone acetate are used with large amounts of sodium chlorides, degenerative lesions in the arterioles of the brain, kidneys, and heart, may result. Because of the physiologically low renal activity during early life, this steroid may cause further depression of this function. It is also theoretically possible to cause atrophy of the adrenal cortex following unwarranted and prolonged administration of this hormone. Because of our limited knowledge of the potent extracts and the possibly dangerous effects upon the patient, it is suggested that under no circumstances should they be used until further investigations have been made by institutions where the patient can be closely studied. Hormone therapy may, in the future, play an integral part in the maintenance of fluid and electrolyte balance in selected cases during early infancy. It is realized that a great deal of research will be required to prove the validity of the concept outlined herein. Further clinical and biochemical investigations are in progress.

#### CONCLUSIONS

1. A theory of physiologic hypofunction of the adrenal glands during the early weeks of life has been presented. Anorexia, failure to gain weight, unexplained tendency to dehydration, attacks of hypoglycemia and protracted diarrhea; one or more of these signs or symptoms originating in the neonatal period and not responding to treatment should be considered as possible manifestations of low adrenal cortical function. These patients may be benefited by hormone therapy.

2. The cases recorded here present a variety of symptoms which are interpreted as signs of low adrenal function. These symptoms rapidly subside after the administration of adrenal cortical hormones. No harmful effects from the injections were encountered.

3. Adrenal hormone therapy may be a necessary adjunct in the maintenance of proper water and electrolyte balance, the preservation of normal intestinal function and the adjustment of a deranged carbohydrate metabolism in selected patients during early infancy.

4. Hypoglycemia during early infancy is not a rare occurrence and it is not uncommonly associated with symptoms of shock.

5. It appears that pork adrenal extract prevents the reappearance of severe hypoglycemia during early infancy.

#### REFERENCES

1. Hartmann, A. F., and Jaudon, J. C.: *J. PEDIAT.* 11: 1, 1937.
2. Butler, A. M., Ross, R. A., and Talbot, N. B.: *J. PEDIAT.* 15: 831, 1939.
3. Wilkens, L., Fleishman, W., and Howard, J. C.: *Endocrinology* 26: 385, 1940.
4. Thelander, H. E., and Chollin, M.: *J. PEDIAT.* 18: 779, 1941.
5. Jaudon, J. C.: *J. Clin. Endocrinol.* 6: 558, 1946.
6. Loeb, R. F.: *Science* 76: 420, 1932.
7. Jaudon, J. C.: *J. PEDIAT.* 28: 737, 1946.



- Althausen, T. L., Anderson, E. M., and Stockholm, M.: *Proc. Soc. Exper. Biol. & Med.* 49: 342, 1939.
- Wilbrandt, W., and Ling-Yel, L.: *Bioch. Z.* 204: 267, 1933.
- Dennis, C., and Wood, E. H.: *Am. J. Physiol.* 139: 182, 1940.
- Clark, W. C.: *Proc. Soc. Exper. Biol. & Med.* 40: 468, 1939.
- Harrison, H. E., and Darrow, D. C.: *Am. J. Physiol.* 125: 631, 1939.
- Swingle, W. W.: *Physiol. Rev.* 24: 1940.
- Tuerkischer, E., and Wertheimer, E.: *J. Endocrinol.* 4: 143, 1945.
- Thaddea, S.: *Med. Klin.* 32: 49, 1936, and 36: 76, 1936.
- Cori, F., and Cori, G. T.: *J. Biol. Chem.* 74: 473, 1927.
- Britton, S. W., and Silvette, H.: *Am. J. Physiol.* 100: 693, 1932, and 118: 594, 1937.
- Long, C. H., Kapzin, B., and Fry, E.: *Endocrinology* 26: 309, 1940.
- Bruch, H., McCune, D. J.: *Am. J. Dis. Child.* 52: 863, 1936.
- Miller, R. A.: *Arch. Dis. Childhood* 16: 230, 1941.
- Collis, W. R. F.: *Brit. Med. J.* 1: 31, 1944.
- Young, W. F., Hallum, J. L., and McCance, R. A.: *Arch. Dis. Childhood* 16: 243, 1941.
- Akerren, Y.: *Acta Paediatrica* 32: 804, 1945.
- Grollman, A.: *The Adrenals*, Baltimore, 1936, Williams & Wilkins.
- Benner, M. C.: *Am. J. Path.* 16: 793, 1940.
- McKittrick, J. D.: *J. PEDIAT.* 16: 151, 1940.
- Ketteringham, R. C.: *Am. J. Dis. Child.* 59: 542, 1940.
- Rushton, J. G., Cragg, R. W., and Stalker, L. K.: *Arch. Int. Med.* 66: 531, 1940.
- Himwick, H.: *Am. J. Digest Dis.* 11: 1, 1944.
- Smith, Clement A.: *The Physiology of the Newborn Infant*, Springfield, Ill., 1945, Charles C. Thomas, p. 268.
- Vogt, M.: *Am. J. Physiol.* 103: 317, 1944.
- Van Creveld, S.: *Am. J. Dis. Child.* 38: 912, 1929.
- Selye, H., Beland, E., and Sylvester, O.: *Exper. Med. & Surg.* 2: 224, 1944.
- Forster, F. M., Cantarow, A., Herbut, P. A., Paschkis, K. E., and Rakoff, A. E.: *J. Clin. Endocrinol.* 6: 77, 1946.

# INTRA-ARTICULAR PENICILLIN TREATMENT OF SUPPURATIVE ARTHRITIS IN INFANTS AND CHILDREN

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ALTHOUGH local treatment of suppurative arthritis with penicillin has been advocated,<sup>1-5</sup> we have been unable to find any detailed reports of such therapy in infants and children; three cases thus treated were briefly mentioned by Herrell and Kennedy<sup>6</sup> in a report on the use of penicillin in pediatrics. The paucity of data prompted this report of four cases of pyarthrosis treated by intra-articular penicillin on the Pediatric service of the New York Hospital between November, 1944, and January, 1946.

## CASE REPORTS

CASE 1.—M. P., a newborn, white female infant, was admitted on Oct. 22, 1944, because of an imperforate anus. Multiple gastrointestinal and genitourinary anomalies were found at operation. On the tenth postoperative day the temperature rose to 38.2° C. and the white cell count was 55,000 with 92 per cent polymorphonuclear cells. Examination disclosed moderate purulent drainage from a cut-down site in the ankle. Blood, nose, throat, and ankle cultures showed a hemolytic *Staphylococcus aureus*. Intramuscular penicillin (10,000 units every three hours, doubled after five days) and sulfadiazine (0.2 Gm. per kilogram per day) were started on the eighteenth postoperative day. After ten days of this intensive combined therapy the left shoulder was noted to be swollen. Roentgenogram showed osteomyelitis with fragmentation of the cortex and periosteal elevation of the head and neck of the humerus.

Aspiration of the shoulder joint released a small amount of pus which contained a hemolytic *Staph. aureus* (Table I). For the twenty-one succeeding days, 8,000 units (10,000 units once, 15,000 units twice) of penicillin in one to 2 c.c. of saline or distilled water were injected daily into the left shoulder joint. Pus was not encountered on all occasions; when present, cultures were positive for hemolytic *Staph. aureus*, even on the twenty-first day of intra-articular therapy. Roentgenogram on the ninth day of topical therapy was interpreted as pyarthrosis with infectious chondritis and early osteomyelitis, and on the eighteenth day as pyogenic arthritis, apparently healing, with destruction of upper end of humerus. Intramuscular penicillin therapy was continued and the blood culture became sterile. Persistence of leucocytosis and fever was attributed to other active foci of infection, renal abscesses.

The extreme resistance of the organism to penicillin was confirmed by in vitro tests (survival of organism in a concentration of 6 units per cubic centimeter). A single intra-articular injection of 15,000 units of penicillin was given on Dec. 13, 1944. The following week three massive doses of 100,000 units in 2 c.c. of water were given intra-articularly at two-day intervals. No pus was obtained for culture. Intramuscular penicillin was discontinued on Dec. 16, 1944, but sulfadiazine was maintained with blood levels of 6 to 8 mg. per cent for three more months. Roentgenograms two weeks after the last intra-articular injection showed distention of the joint capsule with residual osteomyelitis (Fig. 1). No further treatment was given nor were further roentgenograms taken.

The child succumbed to chronic pyelonephritis eleven months later. Although the left shoulder remained larger than the right, there was no limitation in active or passive motion. On gross examination at autopsy, the left humerus and shoulder joint were found to be entirely normal.

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CASE 2.—J. P., a white girl of 5 months, was admitted on Feb. 13, 1945. Three weeks prior to admission the child's right arm was forcibly pulled. The next day she was irritable, had a poor appetite and resented movement of that arm. Her temperature was 38.3° C. On physical examination in the outpatient department two days later, it was noted that she favored the right shoulder, but there were no objective signs. Roentgenogram of the shoulder was negative and the total white blood cell and differential counts were normal. The function of the arm improved, but she ran a persistent, low-grade fever which rose to between 39.4° C. and 40.6° C. during the last three days at home. On the morning of admission the right shoulder became red and swollen. The child appeared acutely ill with a temperature of 38.6° C. The right arm was held in partial abduction and external rotation. There was marked swelling of the deltoid area extending into the neck; the circumference of the right shoulder (around the axilla) being 5½ cm. greater than the left. There was no increased heat or fluctuation. The remainder of the examination was negative.



Fig. 1 (Case 1).—A, Roentgenogram on ninth day of topical therapy. B, Roentgenogram two weeks after last intra-articular injection.

The leucocyte count was 34,200 with 5 per cent lymphocytes, 1 per cent monocytes, 72 per cent mature and 22 per cent immature polymorphonuclear cells. Cultures of the nose, throat and blood showed pneumococcus type VII. Initial roentgenogram showed distention of the right shoulder joint, rarefaction of the proximal metaphyseal end of the humerus and obliteration of the smaller, proximal, epiphyseal center (Fig. 2).

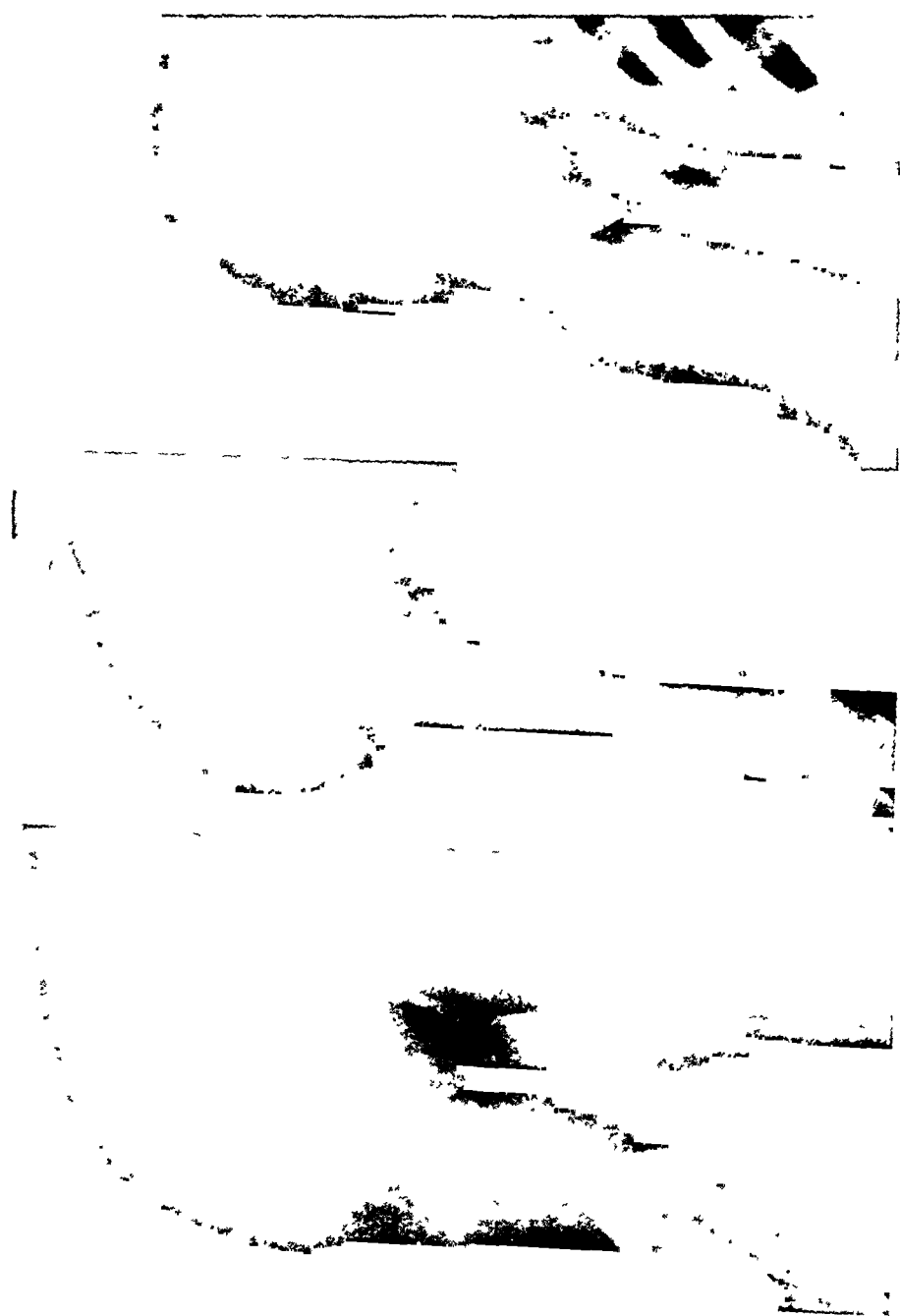


Fig. 2 (Case 2).—A, Roentgenogram on admission. B, Roentgenogram after one week. C, Roentgenogram one year after discharge.

CASES	NAME AND AGE	ORGANISM	JOINT	DURA- TION OF ILLNESS BEFORE ADMIS- SION	BLOOD CUL- TURE	TOTAL UNITS INTRA- ARTICULAR PENICILLIN	INTRA- ARTICU- LAR DOSES (NO.)	OTHER TREATMENT AND DURATION
1	M. P., 10 days	Hemolytic <i>Staph. aureus</i>	Left shoul- der	17 days	Pos.	504,000	25	Sulfadiazine through- out; penicillin I.M. until 4 days before last intra-articular injection
2	J. P., 5 mo.	Pneumo- coccus VII	Right shoul- der	20 days	Pos.	500,000	7	Sulfadiazine from 6th to 20th day; penicil- lin I.M. first 6 days
3	C. S., 3½ yr.	Beta hem- olytic strepto- coccus	Right knee	2 days	Neg.	1,101,000	10	Sulfadiazine 2nd to 15th day; penicillin I.M. first 11 days
4	R. H., 7 yr.	Hemolytic <i>Staph. aureus</i>	Left elbow	3 mo.	Neg.	765,000	8	Penicillin I.M. before admission and 75 days in hospital

The diagnosis of acute pyarthrosis of the right shoulder and osteomyelitis of the adjacent humerus was confirmed by aspiration of the joint which produced 10 c.c. of creamy pus. Smear of the exudate revealed many white cells and intracellular and extra-cellular gram-positive diplococci, proved on culture to be pneumococcus type VII. Sodium penicillin (100,000 units dissolved in 10 c.c. of sterile water) was injected with ease into the joint. Concomitantly, 10,000 units of penicillin were given intramuscularly every three hours.

Aspiration of the joint after thirty-six hours yielded 6 c.c. of pus containing many white cells and a few organisms. In all, penicillin was injected intra-articularly seven times over a period of nine days in doses of 50,000 to 100,000 units dissolved in 2 to 10 c.c. of water, the total dosage being 500,000 units. Intramuscular penicillin was discontinued on the sixth day, and sulfadiazine was begun and continued for the next two weeks in a daily dosage of 0.2 Gm. per kilogram of body weight per day. Blood levels ranged between 4 and 10 mg. per cent. Physiotherapy was confined to hot packs from the eleventh to the twentieth day. Small, whole blood transfusions were administered early in the course as supportive therapy.

All except the first culture of the aspirated pus were negative; no organisms were seen on smear after the fourth treatment. Eight days after the last topical injection, no fluid could be aspirated from the joint. On the sixth hospital day, motion of the shoulder became freer and less painful. Passive motion was painless in one week, and vigorous active motion returned in one month. Serial roentgenograms showed progressive improvement (Fig. 2). The temperature was normal after the first twelve hours. The white blood cell count fell to 17,000 the day after admission, remained between 15,500 and 20,000 with a shift to the left for thirteen days, after which it was normal. Nose, throat, and blood cultures were negative for pneumococcus on the tenth day. Sedimentation rate was normal on the sixteenth day.

The patient was discharged March 16, 1945. The last roentgenogram taken one year after the onset (Fig. 2) showed no abnormality in the joint and minimal thickening of

	INTERVAL BEFORE NORMAL W.B.C.	INTERVAL BEFORE NEGATIVE JOINT CULTURE	DAYS IN HOSPITAL	FOLLOW-UP	
				DURATION	CONDITION
	Never (see his- tory)	About 28 days	401 (see his- tory)	Died at 13 months of chronic pyelonephritis; postmortem examination of joint was nega- tive	
rs	13 days	1 day	30	1 year	General health excellent; afebrile; no local pain or deformity; no limitation of motion in joint; x-ray negative
s	8 days	2 days	30	9 months	General health excellent; afebrile; no local pain or limitation of motion; metaphysis broader in involved leg; x-ray shows rough- ening of articular surface
ys	Never ele- vated	6 days	86	3 months	General health excellent; afebrile; persistent wasting of muscula- ture of arm; extension limited to 170°; still gets physical ther- apy; x-ray shows healing bone and normal joint

the lateral cortex of the upper humerus. When last seen on March 22, 1946, the child was in excellent general health, and there was no pain, deformity, or limitation of motion in the right shoulder.

CASE 3.—C. S., a white girl of 3½ years, had a tonsillectomy and adenoidectomy at another hospital nine days prior to admission. Seven days later she complained of pain in the right leg and felt feverish. She was admitted on May 16, 1945, appearing acutely ill, with a temperature of 40.8° C. Impetiginous lesions were present on the face; the tonsillectomy site was healing. The right knee was hot, red, and swollen, held rigidly at a 90 degree angle, and was extremely painful on motion.

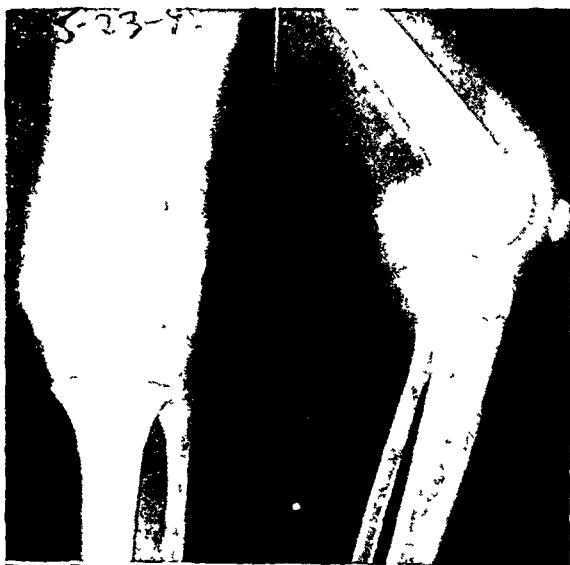
The leucocyte count was 19,000 with 74 per cent polymorphonuclear cells, 10 per cent of which were band forms. Nose and throat cultures produced a heavy growth of beta hemolytic streptococcus; blood culture was sterile. Roentgenogram demonstrated marked distention of the joint space, bulging in the popliteal fossa, and anterior displacement of the patella (Fig. 3).

The joint was aspirated, and 2 c.c. of thick, yellow-green pus was withdrawn which contained beta hemolytic streptococcus by culture; organisms and pus cells were seen on smear. Treatment consisted of daily aspirations and instillations of 100,000 units of penicillin for two days, then 100,000 units in both the medial and lateral compartments of the right knee for four days; the diluent was distilled water in amounts equal to the pus withdrawn and ranged from 2 to 8 c.c. The total intra-articular dose was 1,101,000 units. In addition, penicillin was given intramuscularly, 20,000 units every three hours for a week, then 10,000 units at three-hour intervals for five days. Two blood transfusions were given during the first forty-eight hours.

All cultures from the knee were sterile after the second day, but smears continued to show gram-positive cocci for six days. Afternoon fever of 38.6° C. persisted for eight days after admission; thereafter temperature was normal. The white blood count fell steadily and reached normal on the eighth day. For the first three days the child's gen-

eral condition was critical, but then rapid improvement ensued. Active motion of the leg was achieved on the fifth day; weight bearing was permitted on the tenth day, and after two weeks she could walk alone without pain and with only a slight limp. There was no limitation to passive motion. She was discharged on June 15, 1945, and thereafter received a course of infrared therapy and active passive exercises.

A.



B.



Fig. 3 (Case 3).—A, Roentgenogram on admission B, Roentgenogram nine months after discharge.

The last roentgenogram was taken on March 22, 1946 (ten months after onset), and demonstrated residual irregularity of the articular surfaces. The child has remained well without pain or limitation of motion in the right knee and runs without difficulty. The region over the medial aspect of the metaphysis of the right knee was prominent, and that leg was half an inch greater in circumference than the left.

CASE 4.—R. H., a white boy of 7 years, was in good health until July 20, 1945, when he developed a fever of  $38.9^{\circ}\text{C}$ . and severe pain and swelling of the left elbow. He was put to bed and given salicylates and local heat for one week. The fever subsided but the local pain and swelling persisted. In early August, four intramuscular injections of penicillin in beeswax were given at two-day intervals, 300,000 units per dose. The pain diminished promptly. Despite infrared radiation for one month and alternating ten-day courses of salicylates and sulfadiazine for approximately six weeks, the swelling of the elbow increased and local heat and pain recurred. On Sept. 7 and Sept. 20, 1945, the joint was aspirated; the cloudy fluid was sterile on culture and roentgenogram of the elbow was reported as negative. A cast was applied for two weeks. The patient remained in bed with an evening oral temperature of  $37.5^{\circ}\text{C}$ .

The boy was admitted to the New York Hospital on Oct. 24, 1945, eleven weeks after the onset of the illness. He was well nourished, not appearing acutely ill, with temperature of  $38.3^{\circ}\text{C}$ . There was moderate wasting of the muscle groups of the left arm and forearm. The elbow was swollen, fluctuant, slightly red, and tender about the olecranon. Motion in all planes (including pronation and supination) was limited to 10 degrees.

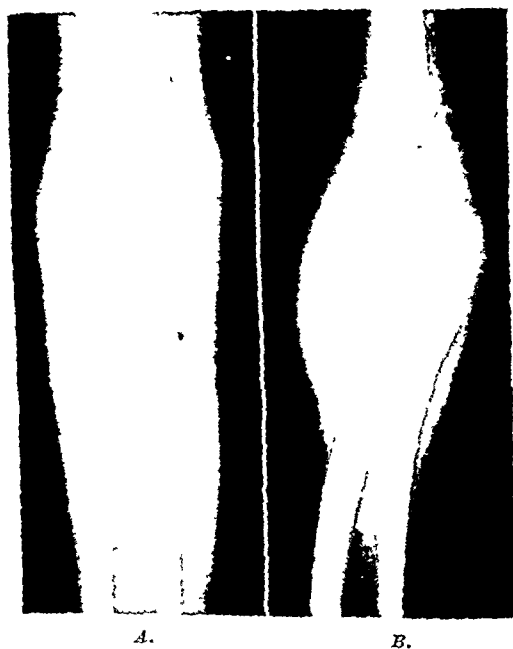


FIG. 4 (Case 4).—A, Roentgenogram on admission. B, Roentgenogram two months after discharge.

Hemoglobin was 10 Gm., red cell count 4,500,000; the leucocytes were 12,200 with 41 per cent polymorphonuclear cells, of which 12 per cent were band forms. Corrected sedimentation rate was 1.45 mm. per minute (normal up to 0.4). Mantoux test and blood culture were negative. Roentgenogram of the elbow on admission showed destruction of the capitellum and trochlea, thickening of the periosteum of the humerus, and fusiform distention of the joint capsule, diagnosed as suppurative arthritis with associated osteomyelitis (Fig. 4). Five cubic centimeters of purulent fluid were aspirated from the involved joint; no organism was observed on smear, but hemolytic *Staph. aureus* was cultured. It was later found to be sensitive to 0.082 units of penicillin per cubic centimeter in vitro.

In the first two weeks the patient was given 10,000 units of penicillin sodium intramuscularly every three hours. Seven joint aspirations were performed, each with replacement by



100,000 units of penicillin in distilled water. Ten days after the last dose of this intensive regimen, aspiration yielded no pus, and 65,000 units were injected, making a total intra-articular dosage of 765,000 units. Intramuscular penicillin was continued for eleven weeks for a total of 8,132,000 units. After the first two aspirations, all cultures and smears were negative. Roentgenographic evidence of improvement was slow. The total white count was normal, but there was persistent elevation of band forms. Sedimentation rate reached a normal level after seventy days. Low-grade fever disappeared after thirty-six days. The arm was never immobilized, and active motion was encouraged. Physical therapy (whirlpool and active-passive exercise) was instituted after the fiftieth day. The return in the range of motion is tabulated in Table II. The boy was discharged on Jan. 18, 1946, after twelve weeks of hospitalization, physical therapy being continued.

TABLE II. IMPROVEMENT IN RANGE OF MOTION FOLLOWING INTRA-ARTICULAR PENICILLIN THERAPY

DATE	DAYS	FLEXION- EXTENSION	PRONATION- SUPINATION
10/24/45	Admission	10 degrees	10 degrees
11/15/45	22	45 degrees	80 degrees
1/ 7/46	75	80 degrees	80 degrees
1/17/46	85	140 degrees	90 degrees
	(Discharge)		
3/26/46	153	170 degrees	90 degrees

The last roentgenogram on April 11, 1946, demonstrated that the capitellum and trochlea were beginning to reform and there was no distention of the joint capsule (Fig. 4). Periosteal proliferation was decreased and general appearance of bone structure improved. There was no evidence of active destructive process. At this time the boy seemed in excellent health and had no complaints. There was still some wasting of the muscle groups of the left arm which exaggerated the bony prominences about the elbow. Extension of the arm could not be performed beyond 170° degrees, but he used that extremity without pain or awkwardness. No other movements were limited.

#### DISCUSSION

*Organism.*—The infecting organisms were all gram-positive: hemolytic *Staph. aureus* in two cases; beta hemolytic streptococcus in one; pneumococcus type VII in one. Blood cultures were positive in two cases. As in the experience with other penicillin-treated infections, hemolytic *Staph. aureus* was the most difficult to manage. The strain in Case 1 was resistant in vitro to penicillin concentrations of 6 units per cubic centimeter.

*Source of Infection.*—In one case (Case 4) no antecedent cause could be identified; whether the pyarthrosis was primary or secondary to osteomyelitis could not be determined. The newborn infant (Case 1) may have developed bacteremia from an infected cut-down site. Osteomyelitis probably preceded the joint infection here and in Case 2, where local trauma initiated the disease. The other case (Case 3) was an uncomplicated pyarthrosis, the blood stream presumably having been invaded from open wounds in the throat or on the face.

*Treatment.*—Intra-articular injections of penicillin in large dosage were continued for as long as pus could be aspirated from the joint, even if previous cultures were negative. When the pus was sterile on culture it was interpreted as being due to the presence of penicillin in the exudate and the resultant inhibition of growth on culture media.

The hazard of undertreatment should be emphasized. Sterilization of the joint was not achieved in the infant (Case 1) with twenty-one daily intra-articular injections of 8,000 units each. The extreme resistance of the organism which was then discovered justified the massive dose (100,000 units) used thereafter. The small amount of diluent (2 c.c.) was determined by the limited amount of pus withdrawn on aspiration. Treatment was discontinued arbitrarily after three such doses with no recurrence. Dosage of this magnitude and in these high concentrations did not increase local discomfort; similar intensive topical therapy has been reported.<sup>7</sup> In Case 4, inadequate therapy at home served only to ameliorate the symptoms and to send the disease into a chronic course. The large total dosage in Case 3 was due to the presence of two noncommunicating pus pockets in the knee, each being treated separately.

Intramuscular penicillin was administered because of the gravity of the disease, the presence of positive blood cultures in two cases, and of osteomyelitis in three cases. Whether systemic therapy is necessary in all cases of pyarthrosis is not definitely determined.

Rammelkamp and Keefer<sup>8</sup> demonstrated penicillin in the blood stream after intra-articular injection, and Bagley<sup>7</sup> has proposed this site as the preferred one for parenteral injection, even in the absence of joint disease. By use of massive dosage he showed that therapeutic blood levels can be achieved. On theoretical grounds, intra-articular penicillin should sterilize the joint directly and the blood stream and other foci of infection secondarily. This remains to be proved clinically. On the other hand, it has been demonstrated by Tillett and associates<sup>9</sup> that intravenous penicillin can sterilize a pneumococcal infection of the joint; and Balboni and associates<sup>10</sup> found that intramuscular penicillin penetrates the joint in a high concentration, disappears slowly, and does not accumulate. These results might imply that aspiration and intra-articular therapy are not necessary. Nevertheless, it would seem preferable to evacuate the pus by aspiration in the presence of pyarthrosis and to allay concomitant discomfort rather than to await spontaneous resorption. The optimal route of administration and dosage is still to be determined.

In three cases oral sulfadiazine was given. The first infant (Case 1) was desperately ill, and all available therapeutic agents seemed indicated. However, the pyarthrosis developed after a three-week course of sulfadiazine. In Case 3, the child remained critically ill after twenty-four hours of penicillin therapy, hence sulfadiazine was added to the therapeutic armamentarium. Sulfadiazine was given late in Case 2 after marked clinical improvement on penicillin alone. We have no definite evidence that sulfadiazine shortened the course of the pyarthrosis in these cases.

The question of the advisability of surgical intervention was raised in Cases 3 and 4 because of the failure of immediate response and the development of separate pus pockets within the same joint in the former and the chronicity of the disease and adjacent osteomyelitis in the latter. A recent paper<sup>11</sup> recommends early surgery as a means of facilitating local instillation of penicillin when pyarthrosis complicates staphylococcal osteomyelitis. However, open drainage increases the likelihood of subsequent limitation of motion

in the joint. Therefore, we preferred to allow a therapeutic trial of intramuscular and intra-articular penicillin first, and were gratified with the outcome both in curing the patients and in restoring full function to the involved joints.

*Course.*—The hospital course was remarkably brief and uneventful, considering the nature of the disease, except in the first patient, who had other complications. In the other three cases, within a week after the first intra-articular dose the children had regained partial use of the affected joint and seemed well on the way to recovery. They were spared immobilization in cumbersome dressings and casts, and the only trauma was from the aspirations. Their general improvement in health was gratifying.

#### SUMMARY

Four cases of suppurative arthritis in infants and children have been presented, in which surgical intervention was not required. Three were in the acute stage of the disease and one in the chronic stage, and adjacent osteomyelitis was present in three. All were treated by joint aspiration and intra-articular instillation of penicillin. Supplemental therapy consisted of intramuscular penicillin in all, oral sulfadiazine in three, transfusions, and physiotherapy.

Three surviving patients were seen after discharge at three, nine, and twelve months, respectively, with complete return of function in the last two and without recurrence in any.

It is suggested on a theoretical basis that intra-articular penicillin therapy alone in large dosage may be adequate.

Acknowledgment is made to Dr. H. Temple and Dr. A. J. Tillinghast of the Department of Roentgenology of the New York Hospital for reviewing the films.

#### REFERENCES

1. Keefer, C. S., and others: J. A. M. A. 122: 1217, 1943.
2. Ravdin, I. S., and Johnston, C. G.: Am. J. M. Sc. 208: 248, 1944.
3. Dawson, M. H., and Hobby, G. L.: J. A. M. A. 124: 611, 1944.
4. Herrell, W. E., Nichols, D. R., and Heilman, D. H.: J. A. M. A. 125: 1003, 1944.
5. Anderson, D. G.: New England J. Med. 232: 400, 1945.
6. Herrell, W. E., and Kennedy, L. J.: J. PEDIAT. 25: 505, 1944.
7. Bagley, W. R.: South. Med. & Surg. 107: 180, 1945.
8. Rammelkamp, C. H., and Keefer, C. S.: J. Clin. Investigation 22: 425, 1943.
9. Tillett, W. S., McCormack, J. E., and Cambier, M. J.: J. Clin. Investigation 24: 595, 1945.
10. Balboni, V. G., Shapiro, L. M., and Kydd, D. M.: Am. J. M. Sc. 210: 588, 1945.
11. Anderson, D. G.: New England J. Med. 232: 423, 1945.

# THE DYNAMICS OF NEWLY BORN BABIES

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THE present paper attempts to lend a hand in the spade work of fact-finding about infantile responses. The term "dynamics" as used in this paper was first employed by Dr. C. Anderson Aldrich, who observed in young infants a specific reaction to an applied force. The muscular energy which the baby releases to resist such force is called "dynamics."

Extensive studies have been carried out in an effort to establish some fundamental facts concerning the dynamics of newly born babies. Two major lines of investigation were followed. First, how do young infants respond to a specific force, in this case a pull on the arms and legs? Second, to what extent is this response influenced by the physical make-up of the child and a variety of factors concerning his delivery?

This study gives an answer to these basic questions only. The wider implications of knowledge of the baby's dynamics can as yet only be surmised. There may be a correlation between what is called dynamics and the inherent emotional qualities of the baby. To shed light on this and establish the meaning of the dynamics of the newly born infant will be the task of further investigation. Follow-up observations are being made on the development of all of the children examined in the present study.

## METHOD

The observations were made in the nursery for newly born infants of the maternity ward at St. Mary's Hospital, Rochester, Minn. Altogether, the dynamics of 689 babies, delivered between February and November, 1944, were determined. Each infant was graded twice. The first test was carried out within twenty-four hours after birth and the second, eight days after delivery. In those cases in which the two tests produced different results the mean figure was established.

Factors which might influence the infant's reactions were examined and statistically evaluated. For the baby these consisted of sex, weight, and pathologic findings. For the mother they included the type of delivery, length of labor, sedation administered during labor, and serious illnesses.

The actual test was simple. The baby was placed on his back on an examining table with his legs apart and his buttocks braced against a small upholstered support. The examiner then held the infant by his hands and forearms and gently lifted him up into a sitting position. Next, the infant was returned to his supine posture and the examiner attempted to straighten his legs with a

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From the Rochester Child Health Project.

slow pull. The child's response was classified according to his resistance to the test. Two extremes were found. At one extreme (Fig. 1) the child did not resist and his body was limp: (1) the head fell back, pulled down by its own weight, (2) the arms were straightened without noticeable resistance from the baby, and (3) the legs followed easily the pull of the examining hand. At the other extreme (Fig. 2) the child resisted and his body showed strong muscular tension: (1) the head was actively lifted up and held, (2) the biceps contracted and the elbow joints formed a sharp angle, (3) the pull on the legs produced an intense contraction at the knee and hip joints.



Fig. 1.—Grade 1 of dynamics.

A scale from 1 to 4 has been adopted for the varying degrees of the babies' resistance. Complete yielding limpness constitutes grade 1 of dynamics. Strong muscular resistance represents grade 4. Grades 2 and 3 accordingly stand for the two intermediate degrees.

#### RESULTS

*Grade Distribution of Total Number of Children.*—When tested for their dynamics, the 689 babies showed a remarkable preponderance of grades 2 and 3 as shown in Table I. The two extremes, grades 1 and 4, represented only 4.6

per cent of the total. At the same time the general tendency was clearly toward the lower rather than toward the higher grades. Most outstanding of all was the small number of infants given top marks with only six infants placed in grade 4.

*Sex in Relation to Dynamics.*—Together, the two middle grades show very little variation as between the two sexes, accounting as they do for 95.8 per cent of the boys and 94.8 per cent of the girls. A somewhat different picture becomes apparent if the two lower "passive" grades are compared with the two higher "active" grades. It then appears that 31.8 per cent of the boys are placed in grades 3 and 4 as against 25.0 per cent of the girls. A more obvious discrepancy between the sexes is seen in grade 4 with its one girl and five boys.

TABLE I. THE DISTRIBUTION OF DYNAMICS ACCORDING TO SEX

DYNAMICS, GRADE	TOTAL		BOYS		GIRLS	
	NUMBER	PER CENT*	NUMBER	PER CENT*	NUMBER	PER CENT*
1	26	4	11	3	15	5
2	465	67	249	65	216	70
3	192	28	116	31	76	25
4	6	1	5	1	1	0.3
Total	689	100	381	100	308	100

\*Percentages based on totals in group.

*Weight in Relation to Dynamics.*—The average weight in grams of the babies in each group was calculated and compared. The weight of the infants in grade 1 averaged 3,183 Gm. The respective figures for grades 2, 3 and 4 were: 3,521 Gm., 3,437 Gm., and 3,583 Gm. The average weight of grades 1 and 2 was 3,503 Gm. and that of grades 3 and 4 was 3,441 Gm.

*Pathologic Findings in Babies and Mothers in Relation to Dynamics.*—The fact that the response of the infants to outside stimuli might have been influenced by their physical status at the time of the test had to be considered. Attention was paid, however, only to illnesses serious enough to interfere with the child's normal activity at that age. All heart murmurs were noted, since an organic heart lesion could not always be excluded. Brain injury (diagnosed by fairly definite symptoms such as one-sided convulsions), Mongolian idiocy, dystrophies, and respiratory difficulties were regarded as possible causes which might interfere with the baby's normal reaction to the applied force of the test.

Examination of Table II shows a clearly marked trend from grade 1 to grade 3. The relative incidence of pathologic findings is highest in grade 1, with 23 per cent in a group of twenty-six. It declines sharply to 4 per cent in grade

TABLE II. DYNAMICS VERSUS BABY'S PATHOLOGIC CONDITION

DYNAMICS, GRADE	TOTAL BABIES	CHILDREN WITH ABNORMALITIES OR THAT DIED							DIED
		TOTAL	PER CENT*	HEART MURMUR	CENTRAL NERVOUS SYSTEM	MONGOLI-AN IDIOT†	ATELECTASIS	RESPIRATORY DIFFICULTY	
1	26	6	23		1	2			
2	465	18	4	12	4	1	1		2
3	192	5	3	2	3			1	
4	6	1	17	1					
Total	689	30	4	15	8	3	1	1	2

\*Percentage based on total number of children who had the grade of dynamics.

†And dystrophy.

2, and 3 per cent in grade 3. Then follows a sudden rise to 17 per cent in grade 4, a rise which, however, is scarcely conclusive, owing to the smallness of the group in this grade. There are only six infants in grade 4 and one of them was found to have a heart murmur. To remove the factor of the small number in the extreme grades, grades 1 and 2 have been added and have been compared with grades 3 and 4. The result is 5 and 3 per cent respectively. In other words, the prevalence of pathologic findings is nearly twice as high in the lower grades as in the higher grades.



Fig 2.—Grade 4 of dynamics.

It was further considered that certain pathologic conditions in the mother at the time of delivery might have had a temporary influence on the behavior of the child (Table III). Toxemia, diabetes, and syphilis in the mother were tabulated for this reason. Here again, as in the infants, the incidence of illness is highest in the lower grades. Ten per cent of the mothers of infants in grades 1 and 2 had pathologic conditions as compared with 5 per cent among those of grades 3 and 4.

TABLE III. DYNAMICS IN RELATION TO VARIOUS PATHOLOGIC CONDITIONS OF MOTHERS

DYNAMICS, GRADE	TOTAL CHILDREN	MOTHERS WITH VARIOUS PATHOLOGIC CONDITIONS				
		TOTAL	PER CENT*	TOXEMIA	DIABETES	SYPHILIS
1	26	4	15	2	2	
2	465	43	9	41	1	1
3	192	9	5	8		1
4	6					
Total	689	56†	8	51	3	2

\*Percentages based on number of children in the group with the particular grade of dynamics.

†Actually fifty-four mothers with pathologic conditions because two of them had more than one pathologic condition.

*Method of Delivery in Relation to Dynamics.*—Since complications during delivery and length of labor might have a transitory or lasting effect on the dynamics of the infant, both these factors were included in the investigation. A distinction was drawn between cesarean section, delivery by forceps, and spontaneous birth. Breech deliveries were classed separately in view of the fact that the breech position of the baby often adds to the difficulties of the birth.

As shown in Table IV, the proportion of spontaneous births to the total of deliveries varies but little and shows no clear trend if each group is considered singly. The number of spontaneous births is eighteen births or 69 per cent of all the births in grade 1, rises to 338 or 72.7 per cent in grade 2 and 147 or 76.6 per cent in grade 3, only to fall again to four births or 67 per cent in grade 4. If grades 1 and 2 are compared with grades 3 and 4, it appears that in the two lower grades the spontaneous births account for 73 per cent of the total deliveries in those grades whereas in the two higher groups this figure stands slightly higher at 76 per cent.

Of twenty-three babies who had breech presentation, three were classed in grade 1 and none in grade 4. On the other hand, a comparison between grades 1 and 2, with their seventeen breech deliveries, and grades 3 and 4, with six, shows that the proportion of breech deliveries in relation to the total number of infants is approximately the same in the two major groups.

Calculations of the length of labor showed the following average figures for each grade: for babies in grade 1 the average length of labor was 489 minutes; for grade 2, 619 minutes; for grade 3, 537 minutes and for grade 4, 555 minutes.

*Sedation Administered During Labor in Relation to Dynamics.*—By far the most important sedatives administered to mothers during labor were pentobarbital sodium (nembutal) and demerol, either combined or separately. Colonic ether was used mainly in conjunction with pentobarbital sodium or demerol or both, while seconal was of very little importance. In ninety-one cases no analgesic agent was administered.

Pentobarbital sodium and demerol combined were employed as sedatives for 248 mothers. As shown in Table V, a higher degree of sedation is recorded in this group for the mothers of babies whose dynamics were graded 3 and 4 than for mothers of babies whose dynamics were of the two lower grades. Exactly the opposite picture is shown by the record of the administration to 223 mothers of pentobarbital sodium alone. Here the average dose was highest for mothers of infants whose dynamics were graded 1 and 2.

For the two most important analgesic agents, therefore, no clear relation was noted between the average doses given to the mother and the dynamics of the infant. The same is true for the other sedatives administered either singly or in various combinations.

*Changes in Dynamics From the First to the Second Examination.*—The first examination of the infant was carried out within twenty-four hours after birth. In order to establish the immutability or inmutability of the results obtained, a second examination was made eight days after delivery. The examiner did not know the result of the first test at the time of the second.



TABLE IV. THE PERCENTAGE DISTRIBUTION OF DYNAMICS ACCORDING TO METHOD OF DELIVERY

DYNAMICS, GRADE	TOTAL CHILDREN	METHOD OF DELIVERY				BRECH PRESENTA- TION (PER CENT†)	
		CESAREAN		FORCEPS			
		A PER CENT*	B PER CENT*	C PER CENT*	D PER CENT*	FORCEPS	SPON- TANEOUS
1	26		31	69	4	8	
2	465	2	25	73	1	2	
3	192	2	22	77	1	2	
4	6		33	67			
Total	689	2	25	74	1	2	

\*Percentages based on total number of children who had the grade of dynamics.

†Included in columns B and C.

TABLE V. SEDATION DURING LABOR CONSIDERED IN RELATION TO DYNAMICS

DYNAMICS, GRADE	PENTOBARBITAL SODIUM			PENTOBARBITAL SODIUM AND DEMEROL				PENTOBARBITAL SODIUM, DEMEROL, AND COLONIC ETHER				PENTOBARBITAL SODIUM AND ETHER			OTHER SEDATION (NO. CASES)
	NO. CASES	GRAINS*	NO. CASES	PENTOBARBITAL SODIUM		DEMEROL (MG.)*	PENTOBARBITAL SODIUM, DEMEROL, AND COLONIC ETHER		PENTOBARBITAL SODIUM AND ETHER		OTHER SEDATION (NO. CASES)				
				NO. CASES	GRAINS*		NO. CASES	DEMEROL (MG.)*	NO. CASES	DEMEROL (MG.)*		NO. CASES	DEMEROL (MG.)*		
1	13	3.7	7	3.9	135.7									4	
2	150	3.5	172	3.8	109.6		4.4	34	138.2	2.9	3.8	3.2	21	59	
3	58	3.2	67	3.9	127.6		4.3	18	191.2	2.9	4.4	2.5	11	27	
4	2	3.0	2	3.0	130.0								1	1	
Total	223	3.4	248	3.8	115.5	2.9	4.4	52	156.5	2.9	4.0	3.0	34	91	

\*Average doses.

\*Average doses.

The grade of dynamics of eighty-seven newborn babies changed somewhat, but the grade of only two of these was altered by more than one point. It should be borne in mind that a very small difference in the behavior of the infant might produce a transfer from one grade to another. On the first test, for instance, the dynamics of a baby might have been classed as being between grades 1 and 2. Having to decide in which of the two grades to place the infant the examiner gave preference to grade 1. On the second test the dynamics of the child might still have been classed between the two grades, but grade 2 chosen.

Relatively, the largest number of changes are recorded in the lowest grade, with fifteen transfers from grade 1 to 2, four from 2 to 1 and two transfers from grade 1 to grade 3. For the two middle grades the changes, though numerically higher, were relatively less frequent, that is, approximately 10 per cent of the total infants in the groups 2 and 3. There were thirty-eight transfers from grade 2 to 3 and twenty-seven from 3 to 2. Only one baby was transferred from grade 3 to 4. A downward trend from the higher grades to the lower is noticeable if the transfers from grades 1 and 2 on the one hand and from grades 3 and 4 on the other are compared. The changes from the two bottom groups to the higher ones amounted to 8 per cent of their original total while in the opposite direction they represented nearly 14 per cent of the infants originally classed in the top grades.

#### COMMENT

The careful observer in a nursery of newborn babies will readily notice a difference in the characteristics of the infants. Aside from their actual physical appearance, the degree of alertness, activity, amount of crying, and interest in nursing vary. The question arises as to whether or not the intensity of such expressions is dependent on an underlying make-up of the emotional constitution of the babies. In the search for a simple measure of the force which may determine the degree with which the baby responds, a reaction specific for each infant was noticed. It is felt that this reaction is an expression of the energy, the dynamics, called forth by the application of outside force. These impressions are not established facts but guides to further study, which in time may permit of more definite conclusions.

Meanwhile, we have had to content ourselves with recording basic observations. They comprised, first, the reaction of the child to the force applied, and, second, the existence of possible influences on such a reaction.

The distribution of the infants in grades of dynamics according to their reaction to the applied force might possibly foreshadow the pattern of adult emotional behavior, in that people who have outspokenly active or passive emotional qualities are fewer in number than those between the two extremes. The statistical result of this initial test, while not conclusive, encourages the hope that a method may have been found to measure the emotional expression of infants.

Perhaps the most relevant finding of our study is the minimal change of dynamics from the first to the second examination. It was determined to be 13 per cent of 689 children. This seems high, if dynamics are thought of as a persistent quality inherent in the infant. But it does not seem high when one con-

siders the influence of environmental factors and the subjectivity of the test. The fact that the dynamic reaction, determined at different times and even by different examiners, remained essentially unaltered, supports the impression that a persistently inherent quality underlies such reactions during the neonatal period.

#### SUMMARY

A study of the dynamics of newly born infants has been made. Six hundred and eighty-nine infants have been examined twice during their eight-day stay in the hospital. Factors which might have influenced their dynamics have been evaluated.

Of 689 infants examined, twenty-six were classified as grade 1 (least active), 465 as grade 2, 192 as grade 3, and six as grade 4 (most active).

The sex distribution showed a prevalence of the boys in the higher grades.

No definite correlation could be established between the babies' weights and their dynamics.

A distinctive influence of pathologic findings in mother and child on the infants' dynamics was observed. The accumulation of serious defects in grade 1 and the absence of serious illnesses in grade 4 are noteworthy.

The relation of the mothers' labor and method of delivery to the grading of dynamics was inconclusive.

The investigations on the decrease and increase of dynamics from the first to the second examination showed a 13 per cent change from one grade to the next one. Two babies made a change of two grades.

The evaluation of the data obtained encourages the hope that dynamics as defined here is an inherent quality and is not decisively altered by outside factors.

# SOME EFFECTS OF INJECTED CYTOCHROME C IN MYOCARDIAL AND CEREBRAL ANOXIA IN MAN

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**A**NOXIA is a problem of widespread clinical interest and has been attacked from many points of view. We have been interested in the possibility of combating the effects of tissue anoxia by enhancing the tissue uptake of oxygen. In this connection we have concerned ourselves more particularly with succinic acid<sup>1, 2</sup> and cytochrome C.<sup>3-5</sup> This report deals with some effects on the heart and brain of the parenteral administration of cytochrome C under conditions of anoxia.

The method used for preparing the cytochrome C was that of Keilin and Hartree.<sup>6</sup> The material obtained by this method was reconcentrated by being put through the 50 per cent ammonium sulfate precipitation a second time. The material was then sterilized by passing it through a Seitz filter. The cytochrome C thus obtained seems to be nontoxic except that on two occasions it has produced a transient urticaria when injected into patients, one of whom had a history of asthma and the other, hay fever. We have found that cytochrome C appears not only to be nontoxic but that it is relatively stable in the body when injected.<sup>7</sup>

Cytochrome C apparently exists in organs in suboptimal amounts. That is to say, there seems to be relatively more cytochrome oxidase present in the organs than is required for activation by the cytochrome C present. Hence, an added supply of cytochrome C could be expected to be effective. We have demonstrated that it is possible in animals to increase significantly the organ content of cytochrome C.<sup>7</sup> The increase in organ content which we could produce following intravenous or intramuscular injection was of a magnitude sufficient to produce an *in vitro* increase in tissue oxygen consumption of 50 to 100 per cent. Hence, we had reason to believe that we might be able to increase the tissue uptake of oxygen in the organs of human beings by the parenteral injection of cytochrome C.

Under normal conditions there would appear to be no purpose in increasing the tissue uptake of oxygen. Under conditions of anoxia, however, such an effect would be highly desirable.

## MYOCARDIAL ANOXIA

A comparatively simple method of studying myocardial anoxia is by means of the electrocardiogram. Anoxic effects on the heart muscle are often reflected in characteristic changes in the electrocardiogram. We therefore selected

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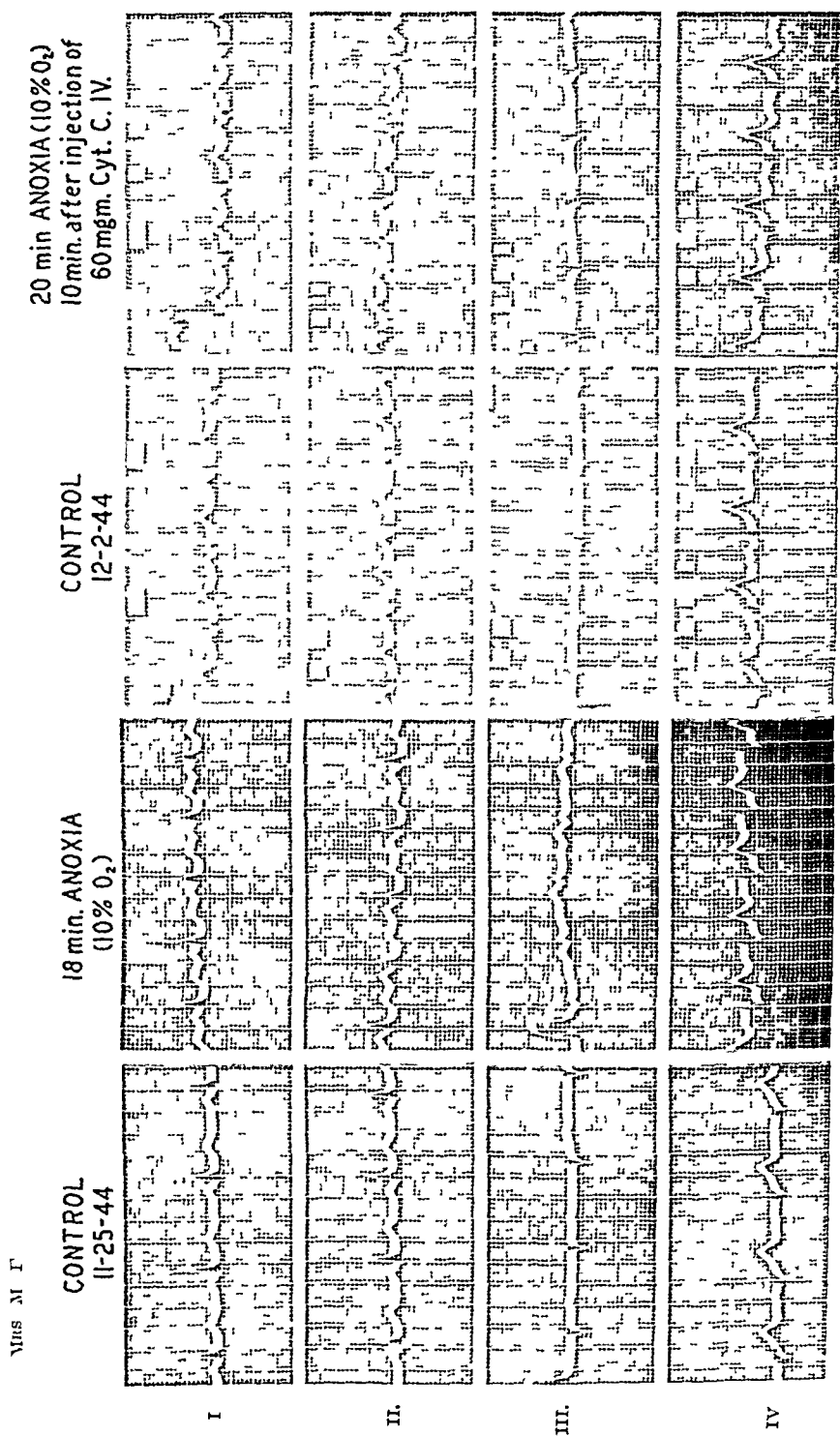


Fig 1.—Effect of cytochrome C in preventing anoxic changes in electrocardiogram. Tracings on left show changes produced by anoxia without cytochrome C. Tracings on right show comparative lack of such changes when cytochrome C had been injected previously.

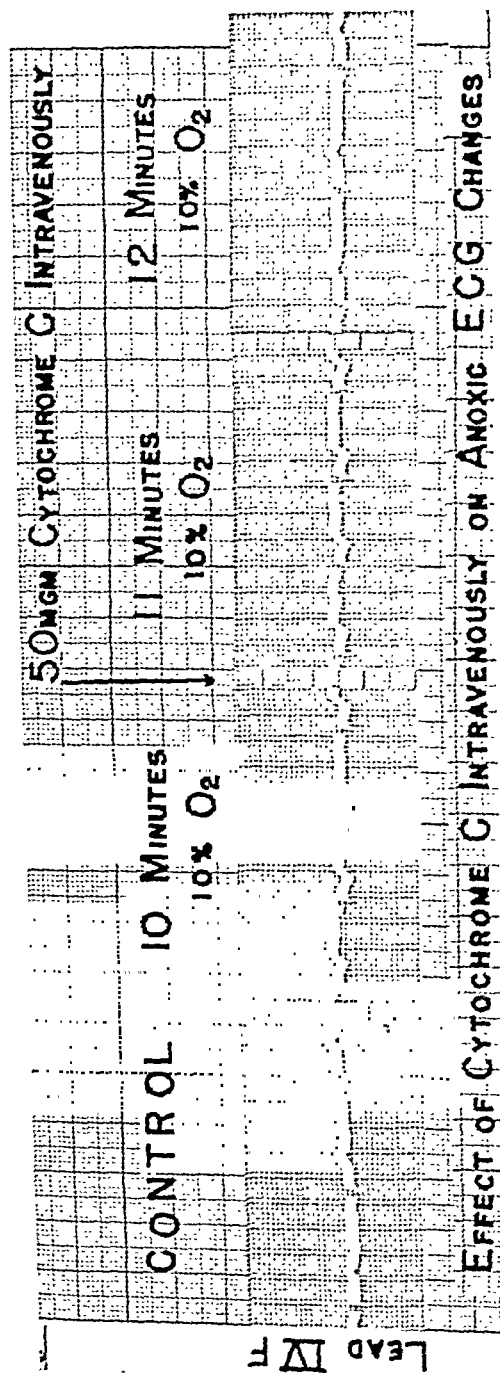


FIG. 2.

four patients who showed striking changes in the electrocardiogram following ten to twenty minutes of exposure to an atmosphere containing 10 per cent oxygen and 90 per cent nitrogen. In these four cases, as indicated by a typical response in the accompanying chart (Fig. 1), the anoxic effects could be prevented by the previous intravenous administration of 60 mg. of cytochrome C. The injected cytochrome C exerts its effect within two minutes, as may be seen in Fig. 2.

In one of the patients in whom the effects of anoxia on the electrocardiogram were studied, the anoxia could not be continued for the full twenty minutes because the patient experienced considerable subjective distress which we took to be cerebral in origin. However, even in this shorter period there were pronounced electrocardiographic changes. When the test was repeated on another day under the same conditions of anoxia, this time after the injection of 50 mg. of cytochrome C intravenously, the anoxia produced no effect on the electrocardiogram; and, what is also important, the subjective disturbances of the anoxia were eliminated and the patient was able easily to continue under the conditions of anoxia for the full twenty minutes. This sequence of events was observed in other patients whether or not there were electrocardiographic changes. That is to say, patients seemed to tolerate the anoxia much more easily if they had previously been injected with cytochrome C than if they had not had the substance. This suggested that the cytochrome C was effective in combating the effects of anoxia on the brain as well as on the heart.

#### CEREBRAL ANOXIA

The measurable effects of cytochrome C on cerebral anoxia were studied through inducing anoxic effects on visual discrimination, and code transliteration. These experiments were done with the very kind cooperation of Drs. W. H. Forbes and J. I. Niven of the Harvard Fatigue Laboratory.

*Effect of Cytochrome C on Visual Discrimination.*—One of the functions which under conditions of anoxia becomes measurably impaired earliest is that of visual discrimination.<sup>10</sup> Two trained subjects were studied, using the Crozier and Holway discriminometer.<sup>11</sup> The results were almost identical in each case and are illustrated in one case in Fig. 3. It will be noted that the cytochrome C succeeds in overcoming completely the anoxic effects. In this figure the differential threshold is plotted against the time at which it was obtained. The subject looked into a binocular microscope head at a dimly illuminated circular field whose intensity was  $\text{Log}_{10} 2.360$ , in milliphotons. After adaptation he was asked to report when he could distinguish a test flash of approximately  $\frac{1}{10}$  of a second superimposed upon the field.  $\text{Log}_{10}$  thus represents the least added intensity in milliphotons at which the subject was able to distinguish the flash. Each point on the chart represents the mean of ten observations. A rise in the threshold represents a deterioration in differential brightness sensitivity and therefore in related visual functions such as acuity. The efficacy of the cytochrome C is indicated by the fact that despite the continuing anoxia, there is a return of the threshold to its normal level as determined in room air.

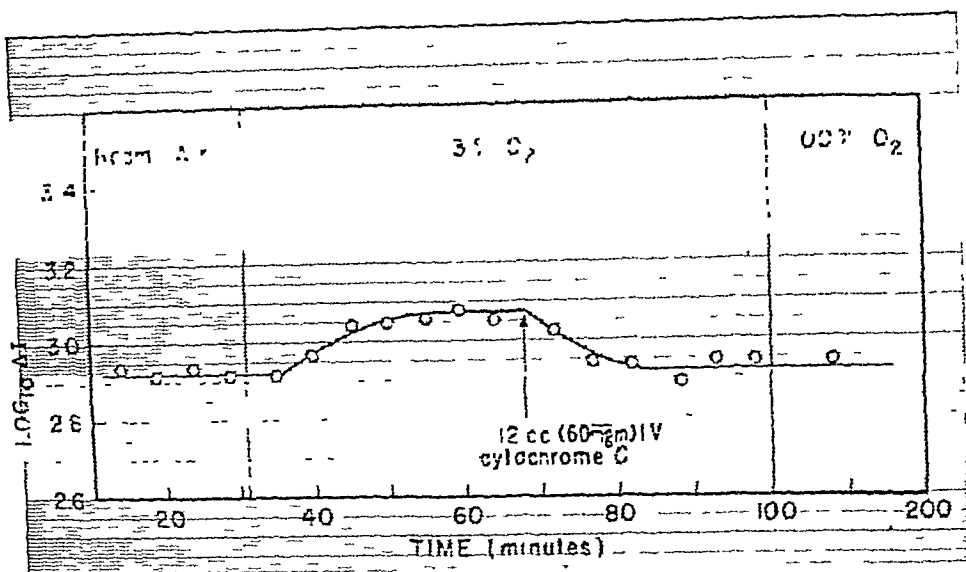


Fig. 3.—Effect of cytochrome C on visual discrimination as shown by chart of reactions of one subject tested.

*Effect of Cytochrome C on Code Transliteration.*—Johnson and Paschal<sup>12</sup> devised a code test which involved the maintenance of visual function, attention, memory, and neuromuscular coordination during a longer period than could be included in an ordinary voluntary spurt. The test has proved of value in measuring the effects of moderate degrees of anoxia. In the test a series of fifty letters to be transliterated must be located in the alphabet and the corresponding letter substituted. On repeated tests, different forms are used so that there is no opportunity for learning. The codes were compiled with a view to insuring the closest practicable approximation to equality of difficulty.

The studies of the effect of anoxia and cytochrome C on code transliteration were carried out in a pressure chamber. The subjects had been fasting for at least twelve hours. The time required for the code transliteration was measured first at sea level, then at a simulated altitude of 16,500 feet before and after the injection of cytochrome, and finally at sea level again. The temperature in the pressure chamber varied between 0° F. to 10° F. so that the subjects required the use of electrically heated suits.

The first experiment was carried out on four subjects. Only two of these subjects showed a definite slowing of time required for the code transliteration at the simulated altitude of 16,500 feet. Hence, it was only these two subjects on whom cytochrome C could exert a correcting beneficial effect. That it did exert such an effect can be seen in Fig. 4. In this chart each point represents the average time of four tests, each test requiring the transliteration of fifty letters into corresponding codes.

On a subsequent occasion the experiment was repeated in these two subjects, but instead of cytochrome C, 5 c.c. of normal saline in one subject and 5 c.c. of 50 per cent glucose in the other were injected intravenously. In these



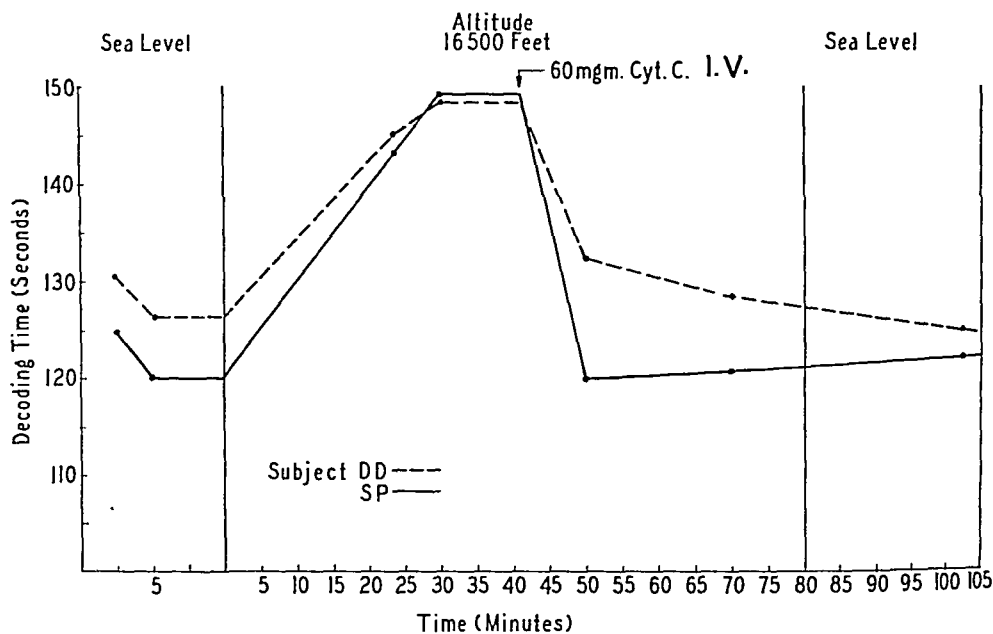


Fig. 4.—Effect of cytochrome C in code transliteration. Each point represents the average time of four tests made on the subjects, each test requiring transliterating fifty letters into corresponding codes.

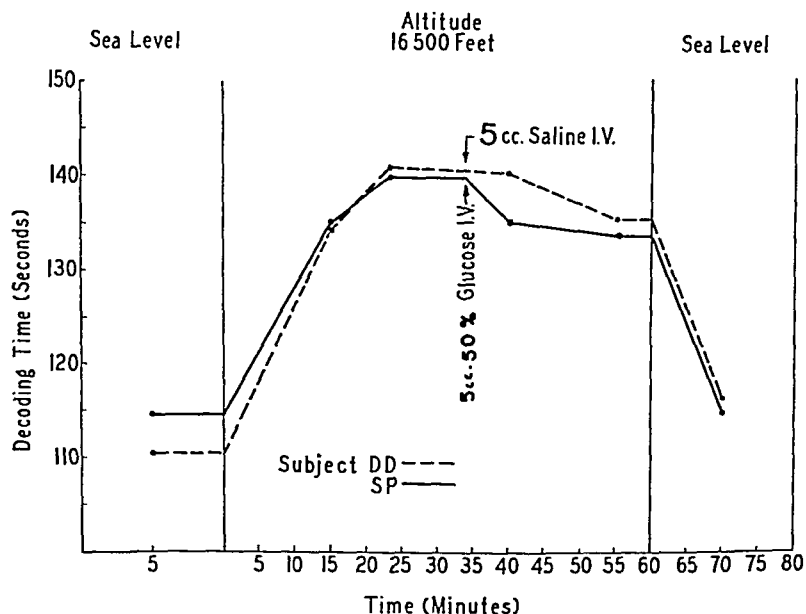


Fig. 5.—Effect of normal saline and 50 per cent glucose on the same subjects tested in Fig. 4.

observations, which served as a control, the saline and glucose had no appreciable effect as can be seen in Fig. 5, although the latter theoretically might have been expected to be somewhat beneficial.

The subjective effects of cytochrome C under conditions of anoxia are worthy of comment. We have indicated previously that following injected cytochrome C, subjects are enabled to tolerate degrees of anoxia which they could not tolerate without the injection. In the experiments in the pressure chamber, this fact was again demonstrated. The general discomfort, mental cloudiness, and torpor induced by the anoxia vanished like a clearing fog within a minute or two after the injection of the cytochrome C. As described by one subject, the sensation was as though a blurred picture were suddenly put into focus. The effect was noted despite the fact that the subjects neither knew what was being injected nor how soon it would be effective.

#### DISCUSSION

Our findings suggest that cytochrome C might be beneficial in clinical conditions associated with myocardial anoxia such as angina pectoris and acute coronary occlusion. The observations which we have made on four patients with angina pectoris through the cooperation of Dr. J. E. F. Riseman indicate that cytochrome C is only moderately effective in increasing the capacity for physical exertion. In the one patient in whom electrocardiograph tracings were obtained during exercise with and without cytochrome C, the changes in the S-T segment induced by exercise without cytochrome C were not observed when cytochrome C had been previously injected. In addition to these observations, made in acute experiments, further observations are desirable in regard to the chronic effect of repeated injections of cytochrome C in angina pectoris. Studies which we have made in patients with intermittent claudication and Raynaud's disease indicate that the effects on muscle ischemia of the continued daily administration of cytochrome C may be quite striking. This has been borne out in early observations on patients with angina pectoris as well.

In three patients with acute coronary occlusion and myocardial infarction, 70 mg. of cytochrome C given intravenously seemed to have no immediate effect either on the electrocardiogram or on the subjective distress. In these cases the failure of cytochrome C to exert a favorable effect may be explained by the fact that it could not reach the infarcted and anoxic tissue because of the vascular occlusion.

Cytochrome C is activated by, among others, the succinic-succinic dehydrogenase system. It might, therefore, be theoretically desirable to supply, with the added cytochrome C in the tissues, an activator like succinic acid. Experiments which we have conducted with a combination of succinic acid and cytochrome C suggest that the cytochrome C effect can, in fact, be enhanced by being so combined with succinic acid.

The possible clinical uses for cytochrome C are as numerous and as varied as the clinical conditions in which anoxia is thought to play a role. In the field of pediatrics, asphyxia of the newborn immediately comes to mind. The possibility of using cytochrome C to enhance the tissue uptake of oxygen is particu-

larly intriguing in conditions associated with cerebral anoxia in view of two facts, namely, (1) that of all organs the brain is probably the most sensitive to oxygen lack; (2) that of all organs the brain has probably the greatest unsaturation of cytochrome C.

#### SUMMARY

1. The effects of anoxia on the electrocardiogram can be prevented by the injection of cytochrome C.
2. Subjects seem to tolerate anoxia more easily when they have been previously injected with cytochrome C.
3. The effects of anoxia in impairing visual discrimination can be overcome by the intravenous injection of cytochrome C.
4. The effects of anoxia in slowing the cerebral functions required for code transliteration can be overcome by the injection of cytochrome C.

#### REFERENCES

1. Proger, S., Aisner, M., and Squires, R. B.: The Prevention of Electrocardiographic Evidence of Myocardial Anoxemia by Chemical Means, *J. Clin. Investigation* 21: 630, 1942.
2. Proger, S.: The Use of Respiratory Catalysts, Particularly Succinic Acid, in Tissue Anoxia, *Bull. New England M. Center* 5: 80, 1943.
3. Proger, S., Dekaneas, D., and Schmidt, G.: The Increase of Cytochrome C Content of Organs Following Its Parenteral Injection, *J. Clin. Investigation* 23: 949, 1944.
4. Proger, S.: Some Effects of Injected Cytochrome C in Animals and Man, *Bull. New England M. Center* 7: 1, 1945.
5. Proger, S., and Dekaneas, D.: Some Further Observations on the Parenteral Use of Cytochrome C With Special Reference to Cerebral Anoxia and Shock, *Bull. New England M. Center* 7: 149, 1945.
6. Proger, S., Dekaneas, D., and Schmidt, G.: The Effects of Anoxia and of Injected Cytochrome C on the Content of Easily Hydrolyzable Phosphorus in Rat Organs, *J. Biol. Chem.* 160: 233, 1945.
7. Proger, S., Dekaneas, D., and Schmidt, G.: Some Observations on the Effect of Injected Cytochrome C in Animals, *J. Clin. Investigation* 24: 864, 1945.
8. Proger, S., and Dekaneas, D.: The Use of Cytochrome C in Combating Tissue Anoxia, *Science*. To be published.
9. Keilin, D., and Hartree, E. J.: Preparation of Pure Cytochrome C From Heart Muscle and Some of Its Properties, *Proc. Roy. Soc., London*, s.B. 122: 298, 1937.
10. McFarland, R. A., Halperin, M. H., and Niven, J. I.: Visual Thresholds as an Index of Physiological Imbalance During Anoxia, *Am. J. Physiol.* 142: 328, 1944.
11. Crozier, W. M., and Holway, A. H.: Theory and Measurement of Visual Mechanisms; Visual Discriminometer Threshold Stimulus Intensity and Retinal Position, *J. Gen. Physiol.* 22: 341, 1939.
12. Johnson, H. M., and Paschal, F. C.: Psychological Effects of Deprivation of Oxygen—Determination of Performance as Indicated by a New Substitution Test, *Psychology* 2: 193, 1920.

# PNEUMOCOCCUS MENINGITIS IN INFANTS AND CHILDREN

## A REPORT ON THE USE OF COMBINED SULFONAMIDE AND PENICILLIN THERAPY

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### INTRODUCTION

PRIOR to the advent of chemotherapy and penicillin, few recoveries from pneumococcus meningitis were reported in the pediatric literature. Waring and Smith<sup>1</sup> reviewed 150 cases with a 100 per cent mortality while Toomey and Roach<sup>2</sup> reported 157 cases with no recoveries. In Children's Hospital, Washington, D. C., there were 66 cases between 1923 and 1939 reported by Lindsay and associates<sup>3</sup> and Grossman,<sup>4</sup> and of this entire series there was only one recovery. Other reports have been similarly discouraging.

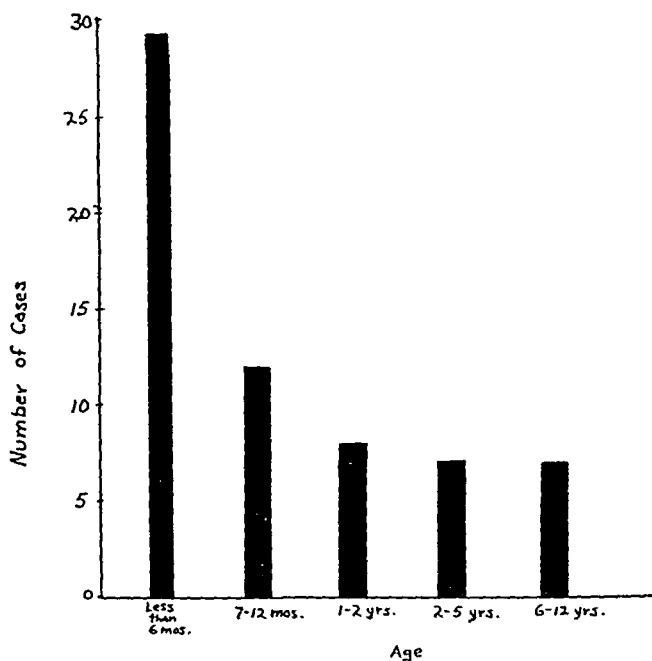
The use of sulfonamide drugs represented a considerable advance in the therapy of pneumococcus meningitis. Between 1940 and 1941 there were 16 cases of pneumococcus meningitis in Children's Hospital; 15 patients died and one recovered; the recovery occurred in a patient who received both sulfadiazine and type-specific antiserum. Of the 15 patients who died, sulfapyridine and antiserum were used in 13 cases while in the other 2, no specific therapy was employed. As a whole, our results with sulfapyridine during this interval were disappointing. In 1942, 8 patients with pneumococcus meningitis were treated, and of this series, 3 recovered and 5 died. Two of the recoveries occurred with sulfadiazine and antiserum and in one case sulfadiazine alone was used. In 1943, 14 patients with pneumococcus meningitis were treated, with 6 recoveries and 8 deaths. Of this group, therapy consisted of sulfadiazine and pneumococcus antiserum in 9 cases, sulfadiazine alone in three cases and no specific therapy in 2 cases. Of the 6 patients who recovered, all received combined sulfadiazine and pneumococcus antiserum therapy; included in the recoveries were 4 patients under 6 months of age. Two of the 6 patients who recovered had blindness and hydrocephalus as residual complications. Of the 8 patients who died, 3 were under 6 months of age, 1 was 16 months and another 20 months of age. In this group, 5 of the 8 deaths occurred within the first twenty-four hours after admission to the hospital; a sixth patient died four days after entry. These results indicated that the initiation of vigorous therapy including sulfadiazine together with pneumococcus antiserum resulted in a significant diminution in the mortality rate. However, the over-all mortality, even with the use of sulfonamide drug and type-specific antiserum, still ranged from 58 to 70 per cent from 1940 to March, 1944, both in our series and in those reported from other institutions, including the report of Hodes and associates<sup>5</sup> from Harriet Lane Hospital. In this regard, Dowling and associates<sup>6</sup> in a review of the results obtained at Galinger Hospital, Washington, D. C., from 1938 to 1941, reported only 4 recoveries

From the Children's Hospital, Washington, D. C.

in 72 cases. All of these patients received sulfonamides, and many received additional specific antiserum. This indicated that prior to the advent of penicillin, the mortality in pneumococcus meningitis was still inordinately high, especially in infants and young children.

In April, 1944, a specific regime of therapy was adopted for pneumococcus meningitis at Children's Hospital, consisting of combined sulfadiazine and penicillin which was to be initiated as soon as the diagnosis was made. The object of the remainder of this paper is to detail the results obtained with this regime since its inception and, in addition, to compare the results with those of previous modes of therapy in the 64 patients seen at Children's Hospital since 1940.

CHART I. AGE DISTRIBUTION OF SIXTY-FOUR PATIENTS WITH PNEUMOCOCCUS MENINGITIS IN CHILDREN'S HOSPITAL FROM JANUARY, 1940, TO JUNE, 1946



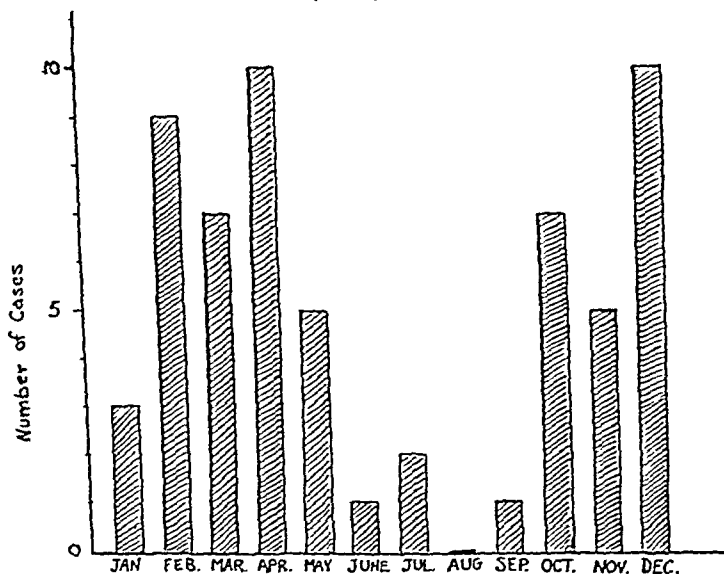
#### SEX, COLOR, AGE, AND SEASONAL DISTRIBUTION

The age distribution is noted in Chart I. Of the 64 patients treated since 1940, 42 were under 1 year of age, and of this number 29 were under 6 months of age. As for the seasonal distribution (Chart II), it will be seen that 58 of the 64 cases occurred between October and May, indicating that the incidence of pneumococcus meningitis coincides with the respiratory season and it is usually a disease of the late autumn, winter, and early spring. Of the 64 patients, 39 were white and 25 Negro; 35 were male and 29 female. Regarding the portal of entry, in 21 patients there was evidence of an associated pneumonia, while in 15 otitis media was present, and in 11 there was an accompanying pharyngotonsillitis. In the other 17 patients there was no obvious portal of entry.

## DIAGNOSIS

a. *Clinical Aspects.*—The symptoms and signs of pneumococcus meningitis in this series are noted in Chart III. Nuchal rigidity, bulging fontanel, and convulsions were present at the time of entry in approximately one-third of the cases. Other prominent findings were lethargy and positive Brudzinski and Kernig signs in approximately one-fourth to one-third of the patients. It is to be noted, especially in the infant age group, that the presence of a bulging fontanel is an important diagnostic finding; in one-half of the 42 patients under 1 year of age a bulging fontanel was present, and in 10 cases it was the only significant finding on physical examination. Of the 21 patients having convulsions at the time of admission, all were under one year of age except

CHART II. MONTHLY DISTRIBUTION OF SIXTY-FOUR PATIENTS WITH PNEUMOCOCCI'S MENINGITIS FROM JANUARY, 1940, TO JUNE, 1946



one 16-month-old-child, indicating that convulsions in the infant group is another important manifestation of meningitis. It is the practice at Children's Hospital to perform routinely a lumbar puncture on every child admitted with a history of fever and convulsions. In the infant age group, signs of meningeal irritation including nuchal rigidity and positive Brudzinski and Kernig's signs were less reliable diagnostically than in the older children. Of these three signs of meningeal irritation the Kernig sign was most equivocal and difficult to interpret. The temperature on admission in these 64 cases ranged between 99 and 107° F. with an average of 103.5° F.

In view of the variation in the signs and symptoms in meningitis, especially in the infant age group, the importance of performing lumbar punctures in any case where doubt exists cannot be stressed too strongly. This is predicated by the fact that the early manifestations of meningitis in the infant age group are often nonspecific, consisting only of fever, fretfulness, vomiting, and

diarrhea. At a time when more overt clinical manifestations of meningitis such as evidence of meningeal irritation become apparent, the disease is often well advanced.

CHART III.—CLINICAL FINDINGS ON ADMISSION IN SIXTY-FOUR CASES OF PNEUMOCOCCUS MENINGITIS

SIGNS	NO. CASES
Nuchal rigidity	26
Bulging fontanel	22
Convulsions	21
Lethargy	20
Positive Brudzinski	19
Positive Kernig	19
Dehydration	12

*b. Laboratory Diagnosis.*—In 35 of the 64 cases, pneumococcus organisms were demonstrated on smear, thus permitting the diagnosis to be made within a short time after lumbar puncture. In the remaining 29 cases the organisms were grown readily on culture. Pneumococcus typings showed that approximately one-half of the cases were represented by types 18, 14, and 6 (Chart IV). It is to be noted that often in pneumococcus meningitis the organisms are present in large number in contrast to meningococcus meningitis, where the number of bacteria is considerably less abundant on smear; however, there are exceptions to this rule. Spinal fluid examinations showed a variation in white cell counts ranging from 80 to 4,500, an average of 1,500 cells per cubic millimeter, with polymorphonuclear cells predominant. In the majority of cases the spinal fluid sugar was substantially reduced or absent, while the protein was usually elevated.

CHART IV. TYPING OF THE VARIOUS STRAINS FOUND IN SIXTY-FOUR CASES OF PNEUMOCOCCUS MENINGITIS AT CHILDREN'S HOSPITAL SINCE 1940

STRAIN TYPE	NO. CASES
18	16
14	8
6	7
7	5
4	4
15	2
19	2
12	2
20	2
3	2
1, 8, 9, 10, 13, 24, and 28	1 each
Undetermined	7

#### THERAPY

Since April, 1944, there have been 19 patients with pneumococcus meningitis who have been treated with combined penicillin and sulfadiazine; type-specific antiserum was used routinely with the first 7 patients in this series, while with the remaining 12 it was omitted. The following therapeutic regime was adopted in these 19 cases.

*a. Penicillin.*—As soon as cloudy spinal fluid was encountered, 5,000 or 10,000 units of penicillin were instilled intrathecally. The penicillin was diluted

in distilled water or saline so that 1,000 units equalled 1 c.c., and an excess of spinal fluid was withdrawn prior to intrathecal instillation. Rammelkamp and Keefer<sup>7</sup> have shown that in adults such a dose of penicillin intrathecally is nonirritating and will remain in therapeutic concentration in the spinal fluid from twenty-four to thirty-one hours. Our own studies in infants and children concur with this observation. In two of the cases in the present series, an increase in the number of cells in the spinal fluid was noted in the fluid withdrawn after the second lumbar puncture. This increase in pleocytosis has been known to result occasionally after intraspinal injection of penicillin, due to meningeal irritation. Penicillin given intrathecally should be introduced very slowly, either by syringe or preferably by gravity, in order to avoid any untoward central nervous system damage such as possible transverse myelitis. After intraspinal injection into the lumbar space and in the absence of blockage, penicillin readily diffuses up into the ventricles, the cerebral and subarachnoid space, and over the convexities of the cerebral cortex. Rammelkamp and Keefer<sup>7</sup> reported the presence of a therapeutic titer of penicillin in the spinal fluid within the skull after lumbar intrathecal instillation. Clinically, no untoward effects were noted from repeated intraspinal injections of penicillin in the present series. It is necessary to maintain careful asepsis in performing this procedure and to change the site of injection frequently in the lumbar region. The advantage of the intrathecal administration of penicillin in pneumococcus meningitis is derived from the fact that a very high concentration can be maintained at the site of infection. In none of the 19 cases was it necessary to administer penicillin into the cisterna magna or into the ventricular space directly. This latter procedure has been recommended by some authors, but the dangers, except when the process is in the most experienced hands, would preclude its widespread use. Cairns<sup>8</sup> recently reported a case of palsy and dysphagia following intraventricular administration of penicillin. Another contraindication to the intraventricular route is that burr holes would be necessary in children whose fontanel had already closed. Any block present in the foramina of Luschka or Magendie or in the subarachnoid space would render valueless the intracisternal mode of administration. In our experience, the lumbar subarachnoid space is the preferred site of intrathecal injection and was used repeatedly in this series. Penicillin was administered by the intrathecal route, usually on a daily schedule. The numbers of instillations ranged from one to twenty, with an average of six injections for each patient. An individual dose of 5,000 units was routinely employed in all but three instances, while the total intraspinal dose of penicillin ranged between 10,000 and 100,000 units, averaging approximately 30,000 units per patient. It was considered expedient to continue the intrathecal administration of penicillin until the spinal fluid had been sterile for from four to six days.

Simultaneously, penicillin was administered intramuscularly on a two- to three-hour schedule. With the exception of two patients, both of whom died within six hours after entry, the total amount of penicillin given intramuscularly in this series ranged between 300,000 and 14,600,000 units, with an average of 2,800,000 units per patient. This amount was administered over the



course of four to thirty days, an average of sixteen days for each patient. It was customary to continue intramuscular penicillin therapy for at least a week and preferably ten days after the temperature had returned to normal. As to the individual dose, it has been our experience that in order to achieve a good therapeutic concentration of penicillin in infants and children, it is desirable to give larger doses than one would expect on a strict weight-for-weight basis. Therefore, 10,000 to 30,000 units every two to three hours was administered, even to the infant age group.

*b. Sulfonamides.*—In the treatment of pneumococcus meningitis, in addition to penicillin, sulfonamides should be given in relatively large doses. Toward this end it has been our practice to use approximately 2 to 3 grains per pound of body weight every twenty-four hours. Before sulfonamides are started, however, an intravenous infusion of either one-sixth molar lactate or 5 per cent glucose in Hartmann's solution is given in quantities approximating 20 c.c. per pound of body weight, in view of the fact that many of the patients are dehydrated and oliguric on entry due to vomiting or inanition. Avoidance of the initial intravenous administration of sulfonamide drug diminishes to a considerable degree the instances of hematuria resulting from crystallization of the drug in the kidney when oliguria is present. Once having initiated a good urinary output, the dangers from hematuria are considerably less. The immediate infusion of crystalloid fluids such as one-sixth molar lactate or 5 per cent glucose in Hartmann's solution has the additional virtue of alkalinizing the urine and initiating the homeostatic acid-base regulatory mechanism of the kidney which is deficient in instances of oliguria and dehydration. No appreciable or significant delay is entailed in achieving an adequate blood-sulfonamide level when the subcutaneous mode of administration is employed rather than the intravenous route. Adequate levels of sulfonamide drug were usually considered to be in the range of 12 to 20 mg. per cent in our cases of pneumococcus meningitis; this was readily achieved by the administration of approximately 2 to 3 grains per pound of body weight in twenty-four hours, given by hypodermoclysis and divided into eight-hour doses. Sulfonamide drug given parenterally as the sodium salt is administered either in one-sixth molar lactate, 5 per cent glucose in Hartmann's solution, or in normal saline as a 1 per cent solution which is nonirritating under the skin. The parenteral mode of administration of sulfonamides was maintained until the patient was able to retain the drug orally. In infants where difficulty may be encountered in administering sulfadiazine in the powdered form by mouth, we have recently used sodium sulfadiazine (in 5 per cent solution) orally, and the infants seemed to tolerate it, receiving the entire dose intended.

Four patients in this series developed hematuria within the first two to four days. However, in view of the urgency of maintaining the sulfonamide drug, it was thought inadvisable to discontinue the drug at that time. Fluids were forced intravenously, by elysis and by mouth. Bicarbonate of soda was administered and the dosage of sulfadiazine was reduced to 1 to 1.5 grains per pound of body weight. In all instances, the hematuria cleared up without any

untoward complications. It would seem that hematuria per se does not constitute a cogent reason for discontinuing sulfonamide drug in cases of pneumococcus meningitis, in view of the fact that discontinuing the drug prematurely may have an untoward effect upon the course of the disease. However, each case has to be individualized. In some instances when hematuria develops, it may be possible to discontinue the drug with impunity, especially when the child is convalescent or the infection is mild. Anuria is a more definite indication for discontinuing sulfonamide therapy than hematuria. Crystalluria is a frequent finding in cases where sulfonamides are used in large doses, but does not seem to be of any real significance and certainly does not constitute an indication for discontinuing the drug. During the acute phase of the infection, it may be deemed advisable to risk the more remote possibility of kidney damage rather than fail to maintain a full measure of therapy against pneumococcus meningitis. In this series, sulfadiazine was maintained for approximately eight to twelve days after the temperature had returned to normal.

*c. Type-Specific Antiserum.*—Since the introduction of sulfonamide drugs and prior to the advent of penicillin, type-specific antiserum was used in approximately one-half of the 80 cases seen at Children's Hospital from 1938 to April, 1944. In comparing the results obtained with sulfonamides alone and combined sulfonamide-antiserum therapy (Chart V) it will be noted that only 5.3 per cent of the recoveries occurred with sulfonamides alone while 21.4 per cent of the recoveries were obtained with combined therapy, suggesting that antiserum contributed substantially to the frequency of recovery in pneumococcus meningitis.

CHART V.—A COMPARISON OF THE RESULTS OBTAINED WITH SULFONAMIDES ALONE AND SULFONAMIDES AND SERUM PRIOR TO THE USE OF PENICILLIN

TYPE OF THERAPY	TOTAL	NUMBER RECOVERIES	DEATHS	PER CENT RECOVERIES
Sulfonamides alone	38	2	36	5.3
Sulfonamides and serum	42	9	33	21.4
Total	80	11	69	

However, in the present series where combined sulfonamide and penicillin therapy was employed, type-specific antiserum was administered only in the first 7 consecutive cases while it was routinely omitted in the next 12 cases. In the 7 cases treated with type-specific antiserum in conjunction with sulfonamide drug and penicillin, there were 6 recoveries and 1 death. Of these 7 patients, 4 were in the infant age group (1 year and under). In the 12 cases where antiserum was omitted, there were 10 recoveries and 2 deaths; however, as will be described later, both of these fatalities occurred within six hours after hospital admission. Of these 12 patients, 7 were infants. The average severity of infection at the time of entry was roughly comparable in both those who received type-specific antiserum and in those in whom it was omitted; therefore, the element of selection was probably minimal. There appeared to be no perceptible difference in course or morbidity in the cases where serum was not used. Because this series is small, it is difficult to appraise the value

of serum as an adjunct in therapy when combined sulfonamide and penicillin is employed. It is possible that combined therapy may have minimized the need for type-specific antiserum. It would probably be safe to omit antiserum at the beginning of therapy and allow its necessity to be determined by the course of the infection.

*d. Supportive Therapy.*—Supportive measures are also indicated, including adequate amounts of fluid to combat dehydration, amino acid preparations, and plasma to repair protein deficit, as well as whole blood. All these have distinct value. The majority of the patients in the present series received at least one whole blood transfusion during the course of their illness.

*e. Heparin and Spinal Fluid Drainage.*—In 5 of the patients (Cases 10, 11, 12, 13, and 16) where it appeared that a chronic basilar meningitis was developing as indicated by varying degrees of spasticity and a viscid spinal fluid with elevated protein, it was deemed advisable to instill heparin intrathecally (1 c.c. per dose) for three or four consecutive days. Simultaneously, spinal fluid drainage was attempted with the substitution of air into the subarachnoid space. This was thought to have the virtue of breaking up any small adhesions that might have occurred and maintaining free flow between the ventricles and the spinal subarachnoid space. In one instance, heparin was discontinued after xanthochromic fluid was obtained, this occurring after 40 mg. or 4 c.c. of heparin had been injected intrathecally over the course of four days. It is impossible to evaluate accurately the role of intrathecal instillation of heparin in this small series. Alexander<sup>9</sup> has used it in 2 cases of *Hemophilus influenzae* meningitis and Signorelli and Friedman<sup>10</sup> in one patient, and both reported some benefit from its use. Of 9 patients with pneumococcus and *H. influenzae* meningitis who received heparin and air intrathecally during the past year at Children's Hospital, it seemed that some improvement did follow its use. Purely on an empirical basis, it would therefore appear advisable to employ the intrathecal injection of heparin and air as a last resort in those instances where development of chronic basilar meningitis is suspected. This is especially important in cases where therapy has been instituted late and where infection has had ample time to produce walled-off pus pockets.

*f. Follow-Up Laboratory Work.*—Daily sulfonamide levels should be obtained during the first week, and for the sake of uniformity it is desirable to obtain the assay about one hour before the next dose is to be administered. The blood levels in this series were maintained between 12 and 20 mg. per cent. A daily urinalysis should be performed to watch for toxic drug effects, especially hematuria. Daily spinal fluid examinations during the acute phase of the disease are singularly helpful in permitting a rather objective evaluation of the patient's course. A decrease in the cell count and protein and an increase in the sugar content can often be construed as favorable prognostic indications. In the series of 19 cases treated with combined penicillin-sulfonamide therapy, spinal fluid cultures became negative on an average of three days after initiation of treatment. However, no penicillinase was added to these spinal fluid cultures, and

this finding may well have represented in part an inhibition of the culture growth of the organism by the penicillin already present in the spinal fluid.

It cannot be stressed too strongly that both sulfonamides and penicillin should be continued for at least eight to twelve days after the spinal fluid has become sterile.

*g. Surgical Intervention.*—As previously noted, otitis media was a frequent associated finding in this series. Resort to the judicious use of surgery in cases of complicating mastoiditis and other foci amenable to surgery is usually regarded as a therapeutic adjunct of primary importance. However, in the current series where combined sulfonamide-penicillin therapy was employed, no mastoidectomies were performed. It is still speculative whether or not our current therapy makes surgical intervention less imperative.

### RESULTS

In 19 consecutive cases of pneumococcus meningitis treated with combined sulfadiazine and penicillin, there were 3 deaths (Chart VI A).

The first fatality (Case 1) occurred in a 1-year-old infant who was admitted in April, 1944, when penicillin was still relatively unavailable. He received sulfadiazine, type-specific antiserum, and supportive therapy for the first six days after admission, and only when his condition appeared to have become critical was penicillin instituted more or less as a terminal measure. The dose was 5,000 units every three hours and he received a total of 60,000 units. The infant died on the eighth hospital day, two days after the initiation of penicillin therapy. No intrathecal penicillin was administered.

The second death occurred in a 12-year-old boy (Case 9), who was admitted to the hospital in a moribund condition after having received a skull fracture involving the anterior fossa and the cribriform plate, with complicating pneumococcal meningitis. The child, prior to entry, had received .25 grain of morphine which might have been contributory to his sudden death. He remained stuporous and died six hours after admission. One dose of penicillin intramuscularly (50,000 units) and one dose of sodium sulfadiazine were administered prior to death.

The third death (Case 19) was that of a 9-year-old girl who was comatose at the time of hospital entry and had a temperature of 106° F. She received one intrathecal dose of penicillin (10,000 units) and two intramuscular injections of 40,000 units at two-hour intervals; in addition, one parenteral dose of sodium sulfadiazine was administered. However, the child never regained consciousness and died six hours after admission.

Thus in two of the three fatalities, death occurred within six hours after admission to the hospital; the rapid terminal progression was such that it precluded an evaluation of the efficacy of combined therapy in both cases. A fair trial of therapy would require a survival of at least twelve to twenty-four hours after its initiation before the effect could be ascertained.

CHART VI A. RESULTS OBTAINED IN NINETEEN CASES OF PNEUMOCOCCIC MENINGITIS

CASE	NAME, AGE, RACE	SYMPTOMS AND SIGNS	DURA- TION OF ILL- NESS BEFORE ADM. (DAYS)	PREVIOUS THERAPY	SPINAL FLUID ON ADMISSION
1	B. S. 12 mo. White	Critically ill; convulsions; tense fontanel; pneu- monia; temperature, 103.6° F.	3	None	Pn.—type 14; 1,180 W.B.C. with 94% P.; sugar, less than 10 mg. %
2	F. B. 6 yr. White	Critically ill; opisthotonos; comatose; meningeal signs; temperature, 104.8° F.	4	None	Pn.—type 18; 270 W.B.C. with 84% P.; sugar, 20-30 mg. %
3	F. W. 5 yr. White	Acutely ill; meningeal signs; temperature 102° F.	5	Sulfonamide, 1 day	Pn.—type 18; 950 W.B.C. with 39% P.; sugar, 0
4	C. B. 12 mo. Negro	Acutely ill; meningeal signs; pneumonia; tem- perature, 103.4° F.	10	Sulfonamide, 8 days	Pn.—type 6; 780 W.B.C. with 75% P.; sugar, less than 10 mg. %
5	J. T. 5 mo. Negro	Acutely ill; convulsions; dehydration; pneumonia; temperature, 104.4° F.	4	None	Pn.—type 28; 790 W.B.C. with 76% P.; sugar, less than 10 mg. %
6	A. E. 3 mo. Negro	Moderately ill; lethargic; otitis media; temperature, 104.4° F.	5	Sulfonamide, 3 days	Pn.—type 6; 156 W.B.C. with 56% P.; sugar, 40-50 mg. %
7	J. T. 13 mo. Negro	Moderately ill; pneumonia; meningeal signs; tempera- ture, 104° F.	2	None	Pn.—type 18; 7,450 W.B.C. with 90% P.; sugar, 20-30 mg. %
8	D. H. 8 mo. Negro	Acutely ill; meningeal signs; bulging fontanel; pneumonia; temperature, 104.2° F.	4	None	Pn.—type 6; 1,500 W.B.C. with 85% P.; sugar, less than 10 mg. %
9	G. B. 12 yr. White	Critically ill; comatose; fractured skull; convul- sions; temperature, 103° F.	2	None	Pn.—type 19; 3,320 W.B.C. with 90% P.; sugar, 40 mg. %
10	M. S. 3 mo. White	Acutely ill; listless; bulg- ing fontanel; meningeal signs; temperature, 103° F.	8	None	Pn.—type 7; 1,520 W.B.C. with 85% P.; sugar, less than 10 mg. %
11	J. F. 11 mo. Negro	Acutely ill; meningeal signs; pneumonia; tem- perature, 105° F.	2	None	Pn.—type 6; 750 W.B.C. with 88% P.; sugar, 20-30 mg. %
12	D. G. 5 mo. White	Critically ill; convulsions; tense fontanel; tempera- ture, 102.6° F.	4	Sulfonamide, 3 days; penicillin, 2 days	Pn.—type 7; 1,150 W.B.C. with 75% P.; sugar, 20-30 mg. %
13	L. F. 4 mo. White	Moderately ill; bulging fon- tanel; temperature, 105° F.	2	None	Pn.—type 14; 4,000 W.B.C. with 89% P.; sugar, 35 mg. %
14	W. G. 14 mo. White	Moderately ill; slight nuchal rigidity; tempera- ture, 101.2° F.	3	Sulfonamide, 3 days	Pn.—type 14; 2,000 W.B.C. with 87% P.; sugar, 40-50 mg. %

## TREATED WITH COMBINED PENICILLIN AND SULFONAMIDE DRUG THERAPY\*

MODE OF THERAPY			ANTI-SERUM	RESULTS	COMPLICATIONS
PENICILLIN		SULFONAMIDES			
INTRATHECAL	INTRAMUSCULAR				
None	5,000 u. q. 3 hr. Total—60,000 u.	Sulfadiazine Gr. 2 to 3/lb./24 hr.	200,000 u.	D.	—
5,000 u. for 11 doses Total—55,000 u.	10,000-30,000 u. q. 3 hr. Total—1,400,000 u.	Sulfadiazine Gr. 2 to 3/lb./24 hr.	300,000 u.	R.	Deafness
10,000 u. for 1 dose	10,000 u. q. 3 hr. Total—300,000 u.	Sulfadiazine Gr. 1 to 3/lb./24 hr.	100,000 u.	R.	None
5,000 u. for 5 doses Total—25,000 u.	10,000 u. q. 3 hr. Total—800,000 u.	Sulfadiazine Gr. 1 to 2/lb./24 hr.	100,000 u.	R.	Spasticity; blindness
5,000 u. for 4 doses Total—20,000 u.	10,000-20,000 u. q. 3 hr. Total—900,000 u.	Sulfadiazine Gr. 2 to 4/lb./24 hr.	200,000 u.	R.	None
5,000 u. for 4 doses Total—20,000 u.	10,000-20,000 u. q. 3 hr.	Sulfadiazine Gr. 1 to 3/lb./24 hr.	250,000 u.	R.	None
5,000 u. for 3 doses Total—15,000 u.	Total—2,400,000 u. 10,000 u. q. 3 hr.	Sulfadiazine Gr. 2 to 3/lb./24 hr.	50,000 u.	R.	None
5,000 u. for 3 doses Total—15,000 u.	Total—760,000 u. 15,000 u. q. 3 hr. Total—1,200,000 u.	Sulfadiazine Gr. 2 to 3/lb./24 hr.	0	R.	None
None	50,000 u.—1 dose	Sulfadiazine 1 dose	0	D. (6 hours after entry)	—
5,000 u. for 20 doses Total—100,000 u.	10,000-15,000 u. q. 2-3 hr. Total—5,100,000 u.	Sulfadiazine Gr. 1 to 3/lb./24 hr.	0	R.	Arrested hydrocephalus; spasticity
5,000 u. for 6 doses Total—30,000 u.	20,000 u. q. 2 hr. Total—3,900,000 u.	Sulfadiazine Gr. 2/lb./24 hr.	0	R.	None
5,000 u. for 8 doses Total—40,000 u.	20,000 u. q. 2-3 hr. Total—3,000,000 u.	Sulfadiazine Gr. 1 to 2/lb./24 hr.	0	R.	None
5,000 u. for 8 doses Total—40,000 u.	20,000-30,000 u. q. 2-3 hr. Total—6,800,000 u.	Sulfadiazine Gr. 2 to 3/lb./24 hr.	0	R.	None
10,000 u. for 1 dose	10,000 u. q. 3 hr. Total—850,000 u.	Sulfadiazine Gr. 2 to 3/lb./24 hr.	0	R.	None

CHART VI A. RESULTS OBTAINED IN NINETEEN CASES OF PNEUMOCOCCIC MENINGITIS

CASE	NAME, AGE, RACE	SYMPTOMS AND SIGNS	DURA- TION OF ILL- NESS BEFORE ADM. (DAYS)	PREVIOUS THERAPY	SPINAL FLUID ON ADMISSION
15	G. R. 17 mo. White	Acutely ill; meningeal signs; tense fontanel; temperature, 103.6° F.	9	Sulfonamide, 3 days	Pn.—type unknown; 533 W.B.C. with 14% P.; sugar, 20-30 mg. %
16	J. J. 6 wk. Negro	Critically ill; marked spas- ticity and opisthotonos; temperature, 104° F.	4	None	Pn.—type 8; 610 W.B.C. with 93% P.; sugar, 0
17	B. M. 9 yr. White	Moderately ill; meningeal signs; temperature, 104.2° F.	3	Sulfonamide, 2 days	Pn.—type unknown; 1,060 W.B.C. with 80% P.; sugar, 10 mg. %
18	P. S. 4 mo. White	Moderately ill; tense fon- tanel; temperature, 103.4° F.	2	None	Pn.—type 1; 1,400 W.B.C. with 89% P.; sugar, 45 mg. %
19	V. F. 9 yr. White	Critically ill; comatose; meningeal signs; tem- perature, 106° F.	3	None	Pn.—type 3; 232 W.B.C. with 90% P.; sugar, 10 mg. %

\*Type-specific antiserum was used in only the first seven cases.

In the 16 remaining cases it was considered that adequate combined sulfonamide drug and penicillin had been employed, and in every case recovery ensued.

It is of some interest to note the age distribution as related to the incidence of recoveries (Chart VIB). Of the 19 patients, 9 were under 1 year of age; of these, there were 7 under 6 months while the other 2 ranged from 6 to 12 months. These 9 infants all recovered in spite of the fact that the duration of illness in the infant group prior to the initiation of combined therapy ranged from two to eight days with an average of three days per patient. This assumes a degree of importance when the usually high mortality rate of this age group is considered. The reason for the hitherto high mortality in infants under 1 year has been variously attributed to a poorer antigenic response and/or greater susceptibility to pneumococcal infections. No less important, however, is the frequent delay in making an early diagnosis in infants because of the paucity of physical findings during that stage of the disease when it is more amenable to therapy.

The conclusion seems warranted that if all the adjuncts in therapy previously outlined are brought to bear as quickly and as vigorously as possible, the prognosis, even in the infant age group, is relatively good.

The youngest patient in this series was a 6-week-old Negro male whose course in the hospital follows.

The infant was admitted with a history of fever and diarrhea of six days' duration. Several episodes of vomiting and drowsiness occurred four days prior to entry. At the time of admission, he was critically ill with marked spasticity, partial opisthotonos, and coarse persistent tremors. The temperature was 101° F. Spinal tap yielded cloudy fluid

## TREATED WITH COMBINED PENICILLIN AND SULFONAMIDE DRUG THERAPY\*—CONT'D

MODE OF THERAPY		ANTI SERUM	RESULTS	COMPLI CATIONS	
PENICILLIN					SULFONAMIDES
INTRATHECAL	INTRAMUSCULAR				
5,000 u for 2 doses Total—10,000 u	10,000 u. q 3 hr. Total—720,000 u	Sulfadiazine Gr. 2/lb./24 hr	0	R	None
5,000 u for 16 doses Total—80,000 u	30,000 50,000 u. q 2 hr. Total—11,600,000 u.	Sulfadiazine Gr. 2 to 1/lb./24 hr.	0	R.	None
5,000 u for 2 doses Total—10,000 u	30,000 u q. 3 hr. Total—2,880,000 u	Sulfadiazine Gr. 2 to 3/lb./24 hr.	0	R.	None
5,000 u. for 2 doses Total—10,000 u	20,000 u. q 3 hr Total—1,760,000 u	Sulfadiazine Gr. 3/lb./24 hr	0	R.	None
10,000 u for 1 dose	40,000 u—2 doses Total—80,000 u	Sulfadiazine 1 dose	0	D. (6 hours after entry)	—

Key Pn, pneumococcus W.B.C., white blood cell count, P. polymorphonuclear leucocytes, R, recovered, D, died

containing 610 white cells with 93 per cent polymorphonuclears; sugar was absent and protein content was 60 mg. per cent. Pneumococcus (type 8) was found on smear and culture

The child received sulfadiazine parenterally (2 to 4 grains per pound body weight) and penicillin, both intramuscularly and intrathecally. The intramuscular dose ranged from 30,000 to 50,000 every 2 hours, and a total dose of 14,600,000 units was administered over the course of four and one half weeks during which penicillin therapy was maintained. The intrathecal dose of penicillin was 5,000 units daily and sixteen intrathecal injections were administered for a total of 80,000 units. In addition, 1 c.c. of heparin intrathecally was given on four consecutive days when it became apparent that a chronic basilar meningitis was developing. Supportive therapy included parenteral fluids, blood transfusions, oxygen, and sedation for persisting convulsions. No type specific pneumococcus anti-serum was used

CHART VII.—RECOVERIES BY AGE IN NINETEEN CASES OF PNEUMOCOCCUS MENINGITIS TREATED WITH COMBINED SULFONAMIDE DRUGS AND PENICILLIN\*

AGE	NUMBER CASES	NO. RECOVERIES	PER CENT RECOVERIES
Less than 6 months	7	7	100
6 to 12 months	2	2	100
1 to 2 years	5	4	80
2 to 6 years	1	1	100
6 to 12 years	4	2	50
Total	19	16	84.2

\*Seven of the nineteen cases received type-specific Antiserum in Addition.

A stormy course in the hospital ensued, punctuated by a complicating urinary tract infection (due to *Bacillus coli*) and persisting diarrhea. The opisthotonos and spasticity gradually disappeared, and after the first week no further convulsive seizures were noted. The spinal fluid became sterile within five days after admission and remained so during



the remainder of the hospital course. The infant was discharged ostensibly well after a six-week hospital stay. The matter of residual central nervous system damage will have to be determined by future follow-ups.

A comparison of the recoveries from pneumococcus meningitis in children under 2 years of age is made with those reported from other institutions (Chart VII); the percentage of recoveries appears to be directly proportional to the incidence of the use of combined penicillin and sulfonamide treatment, less favorable results having been obtained when penicillin alone was used. This is in keeping with Waring and Smith's<sup>1</sup> conclusion that penicillin alone seemed capable of curing the disease in only a relatively small percentage of cases; in other cases, it checked the course of the disease for a limited period but was unable to arrest it completely. It is difficult to say whether penicillin and sulfonamides, used in combination, act by summation or by synergistic action but, whatever the *modus operandi*, combined therapy is the treatment of choice in pneumococcus meningitis.

CHART VII.—ANALYSIS OF PNEUMOCOCCUS MENINGITIS IN CHILDREN UNDER TWO YEARS OF AGE WITH A COMPARISON OF THE RESULTS REPORTED FROM VARIOUS INSTITUTIONS\*

AUTHORS	NO. CASES	COMBINED PENICILLIN AND SULFONAMIDE THERAPY (%)	NO. RECOVERIES	DEATHS	PER CENT RECOVERIES	RECOVERIES WITH RESIDUAL CNS DAMAGE
White and associates <sup>11</sup>	12	14	5	7	41.7	4
Hutchins and Davies <sup>12</sup>	14	64	9	5	64.4	5
Waring and Smith <sup>1</sup>	9	92	8	1	88.8	3
Children's Hospital, Wash., D. C.	14	100	13	1	92.9	3

\*Note the correlation between the incidence of recoveries and the number of cases where combined penicillin and sulfonamide drug were employed.

It is of interest to compare the results obtained with the various types of therapy indicated in Chart VIII in 95 patients with pneumococcus meningitis treated at Children's Hospital since 1933. The gratifying increase in recovery rate since the advent of chemotherapy and penicillin can be clearly noted.

CHART VIII.—TYPES OF THERAPY FOR PNEUMOCOCCUS MENINGITIS BETWEEN JANUARY, 1933, AND JUNE, 1946, CHILDREN'S HOSPITAL, WASHINGTON, D. C.\*

THERAPY	TOTAL	NUMBER RECOVERIES	DEATHS	PER CENT RECOVERIES
Nonspecific	16	0	16	0.0
Serum alone	6	0	6	0.0
Sulfonamide alone	21	2	19	9.5
Sulfonamide and serum	33	10	23	33.0
Sulfonamides and penicillin	12	10	2	83.3
Sulfonamides, penicillin, and serum	7	6	1	85.7
Total	95	28	67	

\*The striking increase in the recovery rate with the advent of combined sulfonamide-penicillin therapy is clearly demonstrated.

In Chart IX, the recoveries from pneumococcus meningitis since 1940 are correlated with age and type of therapy. The 84.2 per cent recovery rate with combined sulfonamide-penicillin therapy is in striking contrast to the 25.6 per cent recovery rate obtained with sulfonamide drugs alone.

CHART IX.—RECOVERIES CORRELATED WITH AGE AND TYPE OF THERAPY IN SIXTY-TWO CASES OF PNEUMOCOCCUS MENINGITIS SINCE 1940\*

AGE	SULFONAMIDE THERAPY			SULFONAMIDE AND PENICILLIN THERAPY		
	TOTAL NUMBER TREATED	NUMBER RECOV- ERIES	PER CENT RECOV- ERIES	TOTAL NUMBER TREATED	NUMBER RECOV- ERIES	PER CENT RECOV- ERIES
Up to 1 year	31	6	19.4	9	9	100.0
1 to 2 years	5	1	20.0	5	4	80.0
3 to 12 years	7	4	57.1	5	3	62.5
Total	43	11	25.6	19	16	84.2

\*The advantage of combined sulfonamide-penicillin therapy over sulfonamide drug alone is evident. Note the 100 per cent recovery rate in the infant age group when combined therapy was employed. The relatively low incidence of recovery in the 3- to 12-year age group is more apparent than real in view of the fact that the 2 deaths in this age group occurred within six hours after admission and did not constitute an adequate trial of the efficacy of combined therapy.

## COMPLICATIONS

In this series, of the 16 children who recovered, 3 had complications. One patient, a 6-year-old boy (Case 2) had residual deafness, while another child, 14 months of age (Case 4), was spastic and appeared to be blind at the time of discharge. A third child, 3 months of age (Case 10), suffered several relapses during his course in the hospital, probably due to premature discontinuation of intrathecal penicillin. This patient received heparin and air intrathecally when it became apparent that a chronic basilar meningitis had developed. A pneumoencephalogram revealed widely dilated lateral ventricles with evidence of moderately advanced hydrocephalus (Fig. 1). The infant eventually recovered from the infection after a protracted course and was discharged with a guarded prognosis. However, when seen on follow-up examination several months later, he had shown remarkable improvement in his mental and physical performance. This serves to emphasize the importance of follow-up studies on infants, who, following meningitis, have shown evidence of incipient hydrocephalus and spasticity. Some of these patients with residual central nervous system damage show considerable improvement in spite of the poor prognosis which is usually entertained at the time of discharge from the hospital. As Hartmann and associates<sup>13</sup> point out, hydrocephalus following meningitis may be due to the failure of absorption of spinal fluid over the cortex because of inflamed meninges, and therefore may be transient in some cases with subsequent regression of the dilatation of ventricles as absorption approaches normal.

It is to be noted that 2 of the 3 patients with complications were ill for eight days before the diagnosis was made and treatment instituted. This serves to re-emphasize the importance of early diagnosis if full recovery without central nervous system sequelae is to be expected.

It is well known that pneumococcus meningitis characteristically produces a viscid exudate of fibrin and pus over the entire brain surface and may readily produce an adhesive arachnoiditis involving the foramina of Luschka and Magendie. This may act as a focus for relapse, and the pus pockets formed may prevent the penicillin from coming in intimate contact with the organ-

isms. The only adequate way of preventing this unfortunate complication is to begin vigorous treatment before the formation of this thick plastic exudate.

The practice of having a bottle of penicillin available at the bedside at the time of initial lumbar puncture has been adopted at Children's Hospital in any case where meningitis is suspected. In the event that the spinal tap yields turbid fluid, penicillin is immediately instilled intraspinally before the nature of the organism is determined. This is based on the premise that it is more important to institute prompt and vigorous therapy in meningitis in view of its gravity than to await a bacteriologic diagnosis before initiating therapy.



Fig 1—M S (Case 10), showing widely dilated ventricles in pneumoencephalogram

There are no clinical signs which enable one to distinguish one type of pyogenic meningitis from another except for the presence of petechiae in the meningococcus type. In addition, it occasionally happens that because of excessive decolorization or poor staining, pneumococcus may be mistaken for meningococcus and vice versa. Also in those cases where *H. influenzae* organisms are present in very small numbers with the predominance of coecal forms, there is the possibility of confusing these forms with either meningococcus or pneumococcus. Intrathecal administration of penicillin is indicated in all types of coecal meningitis and the only instance where its use would be without especial value is *H. influenzae* meningitis. The important consideration, however, is

that vigorous therapy has been instituted quickly if the organism proves to be either pneumococcus or meningococcus. We have all experienced instances where the stained smear was equivocal as to the etiological organism, and where it was necessary to await the results of culture which would not be forthcoming for from twenty-four to forty-eight hours. Such a delay would contribute to a less favorable prognosis since the outcome in meningitis is in no small part predicated by the rapidity with which adequate therapy is instituted.

#### THE NECESSITY OF INTRATHECAL ADMINISTRATION OF PENICILLIN

It is well known that sulfadiazine breaches the blood-brain barrier adequately, and it has been found that the spinal fluid level of sulfadiazine is approximately 60 per cent of the blood level. However, the diffusion of penicillin into the spinal fluid following parenteral administration has been the subject of some controversy in the recent literature. Rammelkamp and Keefer<sup>1</sup> reported that after intravenous administration of penicillin to normal subjects, no demonstrable penicillin was detected in the spinal fluid, indicating that the penicillin administered parenterally failed to cross the arachnoid barrier. These authors suggested that the intraspinal administration of penicillin in meningitis was indicated. Orey and associates<sup>14</sup> similarly reported that no detectable penicillin was present in the spinal fluid following injections of 20,000 to 60,000 units intramuscularly, while McDermott and Nelson<sup>15</sup> administered up to 500,000 units of penicillin intramuscularly and failed to obtain significant titers of penicillin in the spinal fluid. Schwemlein and associates<sup>16</sup> gave massive doses of penicillin parenterally, ranging between 10,000,000 to 25,000,000 units daily, in early syphilis, and found therapeutic spinal fluid levels in the majority of instances. However, this dose is far in excess of the dose usually required in pneumococcus meningitis. On the other hand, Rosenberg and Sylvester<sup>17</sup> administered a comparatively small dose of 20,000 to 40,000 units both intravenously and intramuscularly to 8 subjects with pyogenic meningitis and noted spinal fluid levels ranging from .03 to .35 Florey units per cubic centimeter 60 to 140 minutes later, suggesting that penicillin may be effective in the treatment of meningitis without supplementary intrathecal administration. According to these investigators, the explanation for this disparity might possibly be attributable to the more ready passage of penicillin into the subarachnoid space in the presence of inflamed meninges. The problem has certain practical applications because of the desirability of achieving an adequate spinal fluid level of penicillin at the site of the infection; if this could be achieved by the parenteral route alone, it would preclude the necessity of simultaneous intrathecal administration of penicillin in the treatment of meningitis. Pileher and Meecham<sup>18</sup> have demonstrated that parenteral administration of penicillin without intrathecal administration was inadequate in experimentally induced pneumococcus meningitis in dogs.

A series of penicillin diffusion studies were performed at Children's Hospital to determine whether therapeutic concentrations of penicillin in the spinal fluid could be obtained when varying dosages were given intramuscu-

larly to both normal infants and children and those with inflamed meninges. In addition, an attempt was made to compare the spinal fluid penicillin levels after combined intrathecal and parenteral injections with those obtained after parenteral administration alone.

In the first part of this study, the subjects included 4 patients with tuberculous meningitis, 1 patient with pneumococcus meningitis and 5 with cerebral agenesis without inflamed meninges. These patients weighed between 16 and 60 pounds and the dosage given intramuscularly varied between 10,000 and 50,000 units. Spinal fluid assays were performed one, two, and three hours, respectively, after the intramuscular injection of the penicillin.

CHART X.—PENICILLIN SPINAL FLUID LEVELS AT ONE- TO THREE-HOUR INTERVALS AFTER INTRAMUSCULAR INJECTION OF VARIOUS DOSAGES

SUBJECT	WEIGHT (LB.)	DIAGNOSIS	PENICILLIN DOSE I.M. (UNITS)	SPINAL FLUID PENICILLIN LEVELS AFTER I.M. INJECTION (FLOREY UNITS/C.C.)		
				1 HOUR	2 HOURS	3 HOURS
1	16	Cerebral agenesis	10,000	0	0	0
1	16	Cerebral agenesis	10,000	0	0	0
2	23	Cerebral agenesis	10,000	0	0	0
2	23	Cerebral agenesis	10,000	0	0	0
3	30	Tuberculous meningitis	25,000	0	0	0
4	35	Tuberculous meningitis	25,000	0	0	0
5	38	Tuberculous meningitis	25,000	.078	.039	.020
6	60	Pneumococcus meningitis	30,000	0	0	0
7	32	Tuberculous meningitis	50,000	.156	.078	.039
8	25	Cerebral agenesis	50,000	0	0	0
9	30	Cerebral agenesis	50,000	0	0	0
10	34	Cerebral agenesis	50,000	0	0	0

It will be noted in Chart X that in only 2 out of 10 cases were significant spinal fluid titers of penicillin noted after intramuscular injection. One of these, a child with tuberculous meningitis (Subject 5) after 25,000 units of penicillin intramuscularly, showed a titer of .078, .039, and .02 Florey units, respectively, at the end of one, two, and three hours. The second child, also with tuberculous meningitis (Subject 7) showed a therapeutic concentration in the spinal fluid after 50,000 units intramuscularly. It was interesting to note that the patient with pneumococcus meningitis (Subject 6) showed no demonstrable spinal fluid titer of penicillin after 30,000 units intramuscularly. These results would seem to indicate that infants and children, like adults, show poor diffusion of penicillin across the blood-brain barrier, and in order to insure adequate therapeutic concentrations in the spinal fluid it is not possible to rely upon the parenteral administration alone.

In the second portion of this study, an attempt was made to determine the longevity of a demonstrable penicillin titer in the spinal fluid after one dose intrathecally in children. Toward this end, 5,000 units were instilled intraspinaly in 4 subjects and spinal fluid levels were determined at intervals ranging between eleven and twenty-four hours after the intrathecal injection (Chart XI). It was found that in the 4 cases, a titer ranging from .039 to 0.078 Florey units was present at the end of the intervals noted. This is essentially in agreement with the results obtained in adults by Rammelkamp and Keefer<sup>7</sup>

who found therapeutic concentrations still present at the end of twenty-four to thirty-one hours after a single intrathecal injection of approximately 10,000 units.

CHART XI.—ILLUSTRATING SPINAL FLUID PENICILLIN LEVELS AT VARIOUS TIME INTERVALS FOLLOWING INTRATHECAL ADMINISTRATION OF PENICILLIN

SUBJECT	WEIGHT	INTRATHECAL DOSE	TIME INTERVAL AFTER PENICILLIN ADMINISTRATION	SPINAL FLUID LEVEL (FLOREY UNITS/C.C.)
1	20	5,000 units	11 hours	.039
2	25	5,000 units	12 hours	.078
3	28	5,000 units	24 hours	.039
4	22	5,000 units	24 hours	.078

In the third portion of this study, spinal fluid penicillin assays were performed on 5 children with pyogenic meningitis during the course of therapy. These children were receiving a daily intrathecal injection of penicillin of either 5,000 or 10,000 units, together with 20,000 units of penicillin intramuscularly every two hours. The spinal fluid assays were performed at intervals of nine to twenty-four hours after the institution of therapy to determine the nature of the levels obtained with this recommended mode of penicillin administration, i.e., a combination of intrathecal and intramuscular injections. It was found that in all cases adequate titers were present at the end of the stated intervals, ranging from .039 to .312 Florey units per cubic centimeter (Chart XII). This would indicate that probably only one intrathecal dose of penicillin is required per day in infants and children.

CHART XII.—ILLUSTRATING SPINAL FLUID PENICILLIN LEVELS AT VARIOUS TIME INTERVALS FOLLOWING BOTH INTRATHECAL AND INTRAMUSCULAR ADMINISTRATION OF PENICILLIN

SUBJECT	WEIGHT (LB.)	DIAGNOSIS	PENICILLIN (UNITS)		TIME INTERVAL (HR.)	SPINAL FLUID LEVEL (FLOREY UNITS/C.C.)
			INTRATHECAL	INTRAMUSCULAR (Q 2 HR.)		
1	30	Pneumococcus meningitis	5,000	20,000	9	.078
2	22	Pneumococcus meningitis	5,000	20,000	12	.312
3	18	Pneumococcus meningitis	5,000	20,000	24	.039
4	24	Meningococcus meningitis	5,000	20,000	24	.312
5	16	Meningococcus meningitis	10,000	20,000	24	.156

The conclusion seems warranted that combined intrathecal and intramuscular injections of penicillin in children offers the optimal means of obtaining satisfactory concentrations of penicillin in the spinal fluid in all cases, and would be the method of choice in treating penicillin-susceptible pyogenic meningitis.

#### CONCLUSIONS

1. Nineteen infants and children with pneumococcus meningitis were treated with combined sulfonamide and penicillin therapy. Of this number, 16 recovered and 3 died. Two of the deaths occurred within six hours after entry. Three of the patients who recovered showed residual central nervous system sequelae.

2. Diffusion studies performed on infants and children indicate that penicillin should be administered both intramuscularly and intrathecally to achieve therapeutic spinal fluid penicillin concentrations in meningitis.

3. Sulfadiazine was used in conjunction with penicillin in the present series. The combination of both drugs appears to offer definite advantages over penicillin alone. Therapy should be continued for at least eight to twelve days after sterilization of the spinal fluid.

4. Of the 19 patients receiving combined sulfonamide-penicillin therapy, type-specific antiserum was administered only to the first 7 patients while it was routinely omitted to the next 12. Of the 7 receiving antiserum, there were 6 recoveries and 1 death, while in the 12 where antiserum was omitted, there were 10 recoveries and 2 deaths. Because the series is small, it is difficult to appraise the value of antiserum as an adjunct in current therapy. It is possible that combined sulfonamide-penicillin treatment may have minimized the need for type-specific antiserum.

5. Heparin was administered intraspinally in cases where chronic basilar meningitis developed, and was thought to have some value in the treatment of this complication.

6. The importance of the early institution of therapy in pneumococcus meningitis cannot be overemphasized. If all the measures in present-day therapy are brought to bear as quickly and as vigorously as possible, the prognosis, even in the infant age group, is relatively good.

We are greatly indebted to Dr. E. Clarence Rice for his invaluable help in the supervision of the treatment of these patients. We also wish to express our appreciation to Drs. Joseph S. Wall and P. A. McLendon for their helpful suggestions and advice. Dr. Morton Johan and Miss Miriam Leetch rendered valuable aid in the accumulation of data for this paper.

#### REFERENCES

1. Waring, A. J., and Smith, M. H. D.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcal Meningitis, *J. A. M. A.* 126: 418, 1944.
2. Toomey, J. A., and Roach, F. E.: Pneumococcus Meningitis, *Ohio State M. J.* 35: 841, 1939.
3. Lindsay, J. W., Rice, C. E., and Selinger, M. A.: Meningitis in Children—A Review of 331 Cases, *Med. Ann. District of Columbia* 6: 231, 1935.
4. Grossman, A. M.: Pneumococcal Meningitis in a Three Months Old Infant With Recovery, *Arch. Pediat.* 57: 355, 1940.
5. Hodes, H. L., Smith, M. H. D., and Ickes, H. J.: Sixty Cases of Pneumococcal Meningitis Treated With Sulfonamides, *J. A. M. A.* 121: 1334, 1943.
6. Dowling, H. F., Dauer, C. G., Feldman, H. A., and Hartman, C. R.: Pneumococcal Meningitis: A Study of Seventy-Two Cases, *New Eng. J. Med.* 226: 1015, 1942.
7. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, *J. Clin. Investigation* 22: 425, 1943.
8. Cairns, H., Duthie, E. S., Lewin, W. S., and Smith, H. V.: Pneumococcal Meningitis Treated With Penicillin, *Lancet* 1: 655, 1944.
9. Alexander, H. E.: Treatment of Type B Hemophilus Influenza Meningitis, *J. PEDIAT.* 25: 517, 1944.
10. Signorelli, J. J., and Friedman, L. L.: Penicillin and Heparin in the Treatment of Pneumococcal Meningitis: Case Report, *South. M. J.* 38: 776, 1945.
11. White, W. L., Murphy, F. D., Lockwood, J. S., and Flippin, H. F.: Penicillin in the Treatment of Pneumococcal, Streptococcal and Staphylococcal Meningitis, *Am. J. M. Sc.* 210: 1, 1945.
12. Hutchins, G., and Davies, J. A. V.: Penicillin Treatment of Pneumococcus Meningitis in Infants, *J. PEDIAT.* 27: 505, 1945.

13. Hartmann, A. H., Love, F. M., Wolff, D., and Kendall, B. S.: *Diagnosis and Management of Severe Infections in Infants and Children: A Review of Experiences Since the Introduction of Sulfonamide Therapy, Pneumococcus Meningitis*, *J. PEDIAT.* 27: 118, 1945.
14. Orey, E. M., Meads, M., Brown, B., Wilcox, C., and Finland, M.: *Penicillin Levels in Serum and in Some Body Fluids During Systemic and Local Therapy*, *J. Lab. & Clin. Med.* 30: 809, 1945.
15. McDermott, W., and Nelson, R. A.: *The Transfer of Penicillin Into the Cerebrospinal Fluid Following Parenteral Administration*, *Am. J. Syph., Gonorr., & Ven. Dis.* 29: 403, 1945.
16. Schwemlein, G. X., Barton, R. L., Bauer, J. J., Lowe, L., Bundesen, H. N., and Craig, R. M.: *Penicillin in Spinal Fluid After Intravenous Administration*, *J. A. M. A.* 130: 340, 1946.
17. Rosenberg, D. H., and Sylvester, J. C.: *The Excretion of Penicillin in the Spinal Fluid in Meningitis*, *Science* 100: 132, 1944.
18. Pilcher, C., and Meacham, W. F.: *The Treatment of Pneumococcal Meningitis by Intrathecal Administration of Penicillin*, *J. Neurosurg.* 1: 76, 1944.



## INTRAVENOUS ALIMENTATION OF INFANTS

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**V**ENOCLYSIS for restoration of hydration and electrolyte balance and maintenance of fluid equilibrium for periods of two or three days and occasionally for longer periods of time has become a part of everyday pediatric practice. No attempt is usually made to provide a sufficient caloric intake during such periods. Increased understanding of metabolic changes in starvation and dehydration, increased availability of sources of nitrogen such as plasma and casein hydrolysates, and improved methods in technique of venoclysis have made adequate alimentation for extended periods of time by means of continuous intravenous clysis both desirable and practicable. The first reports of the successful employment of long periods of parenteral alimentation using, in most instances, casein hydrolysates combined with solutions of glucose, electrolyte, and vitamins, were made by surgeons and concerned adult patients. In most instances, one or more infusions over a period of several hours were given daily. Elman<sup>1</sup> in 1940 reported in detail on eight cases in which no food was given by mouth, but nitrogen retention was achieved or nitrogen loss greatly decreased over periods up to fifteen days by the use of daily injections of a maximum of 9.6 Gm. of nitrogen given as casein hydrolysate, and enough glucose to bring the caloric intake to a maximum of 1,600 calories. Brunschwig and associates<sup>2</sup> markedly reduced the nitrogen loss in three patients for periods of twenty-three days by intravenous alimentation alone. He maintained one patient in positive nitrogen balance for a period of ten days by the use of 3 Gm. of protein and thirty-five calories per kilogram of body weight. A second patient<sup>3</sup> was maintained in positive nitrogen balance and a weight gain achieved by the use of fat, glucose, and an amino acid mixture administered intravenously for seventeen days. Recently, Brunschwig and associates<sup>4</sup> reported a period of eight weeks of successful intravenous nutrition with casein hydrolysate, dextrose, saline, and vitamins. The patient remained in excellent health but lost 12.5 kg. of weight during the period of withdrawal of oral feeding. In infants, the small caliber of the veins, the great difficulty of preserving asepsis, and the marked lability of fluid and mineral equilibrium make the procedure technically much more difficult than it is in adults. Continuous venoclysis almost always has to be employed for as long as the parenteral alimentation continues, and different veins must be used every few days because of thrombosis of the vein and swelling of the adjacent tissues. Hartmann and his co-workers<sup>5</sup> reported successful intravenous alimentation in infants for periods of three days. They maintained a 6-year-old girl with tetanus in a good state of nutrition for fourteen days, during which time she lost only 0.5 kg. of weight. Helfrick and Abelson<sup>6</sup> gave complete intravenous feeding to a marantic

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infant ill with Hirschsprung's disease. They used fat, carbohydrate, and an amino acid mixture. At the end of five days the fat pads in the cheeks and fat over the ribs had returned and the general nutrition was markedly improved. The baby was able to take sufficient food by mouth to maintain his improved nutrition after this time.

This report deals with experience acquired during the last year and a half with the administration to infants by venoclysis of all, or the majority of, the needed elements of nutrition for periods up to fifteen days. Most of the children suffered from chronic or recurrent diarrhea and vomiting. The aim was to supply adequate fluid and salts, and at least maintenance amounts of calories and protein. Of necessity, somewhat arbitrary figures had to be chosen as representing basal requirements. A total fluid intake of 150 c.c., 50 calories, and 2 Gm. of protein per kilogram of body weight was elected. The saline value was calculated on the basis of Butler's figures<sup>2</sup> as 80 c.c., with an addition of 5 c.c. for each kilogram of body weight. In malnourished infants or those in whom clyses were continued for long periods of time, the attempt was made to furnish sufficient protein and calories to produce actual weight gain. To such infants were given amounts of protein and calories approaching, or at times exceeding, those usually contained in formula feedings, that is, two or three times the minimal standard. Vitamins were generously supplied throughout. Fat was not provided. In dehydrated infants, information on electrolyte and total osmotic equilibrium was obtained by means of carbon dioxide, chloride, and nonprotein nitrogen determinations. These were made at the outset of therapy and repeated as often as indications arose. Such determinations are of particular importance in cases of diarrhea, in view of the wide variety of patterns of electrolyte and osmotic derangements which are apt to be encountered. The type of fluid administration was adjusted to correct imbalances where found. Upper limits were not set for fluid intake, as we found that no harm ensued from the administration of large amounts of fluid, provided that salt intake was controlled.

In order to avoid the untoward effects of excessive electrolyte administration, the attempt was made to provide the lowest amount of salt compatible with good hydration of the infants. Since under such a plan the chloride rather than the sodium intake becomes the limiting factor, all estimates of the salt content of parenteral fluids were based on their chloride content. Physiological saline was taken as the basis of calculation. In this solution, sodium and chloride contents are equal. In plasma, particularly when citrated, the chloride value is close to one-half that in physiological saline. Sodium bicarbonate and lactate which do not contain chloride were not considered in these calculations.

In the first twenty-four hours, depending on the degree of hydration, saline-containing fluid in amounts equal to 5 to 10 per cent of the body weight in addition to the basal requirement was given. Subsequently, when diarrhea continued, one and one-half to two times the basal amount of electrolyte was supplied. To premature and very young infants in whom high chloride values in the plasma were observed, probably owing to small loss of chloride with diarrheal stools, less salt-containing fluid was given for correction of dehydration and

maintenance. Initially, in order to avoid embarrassment of the circulation of severely dehydrated patients by the use of hypertonic solutions, 50 to 100 c.c. of physiological saline were administered rapidly. The acidosis was then corrected by 3.7 per cent sodium bicarbonate solution. In patients with mild acidosis, sodium lactate was used when correction was indicated. In most cases blood, plasma, casein hydrolysate, and hypertonic solutions of glucose or glucose in saline were administered by means of a slow intravenous drip only when dehydration was largely overcome. In cases of severe circulatory collapse, extreme malnutrition, or anemia, blood and plasma were occasionally given in the first twenty-four hours. The frequent occurrence of hypocalcemia with attendant symptoms during the postacidotic phase, a subject to be discussed in a subsequent paper, led to the use of oral or parenteral calcium therapy.

CHART I. SUMMARY OF INTAKE OF FLUIDS, CALORIES, SALT, AND PROTEIN OF PATIENTS ON PARTIAL OR TOTAL PARENTERAL THERAPY

Directions:

Enter cubic centimeters of oral, subcutaneous, and intravenous intake in upper left corner of appropriate box.

Enter calories in lower right corner.\*

DATE	FOODS AND BEVER- AGES† C.C./CAL.	NaHCO <sub>3</sub> LACT. C.C.	GLUCOSE IN WATER‡ C.C./CAL.	GLUCOSE IN SALINE§ C.C./CAL.	PHYSI- OLOG- ICAL SALINE C.C.	PLASMA BLOOD C.C./CAL.	AMIGEN IN GLUCOSE C.C./CAL.	TOTAL INTAKE		
								FLUID C.C./CAL.	SALINE VALUE§ C.C.	PRO- TEIN   GM.

\*Calories: 5 per cent glucose,  $0.2 \times$  cubic centimeters; 10 per cent glucose,  $0.4 \times$  cubic centimeters; amigen,  $0.6 \times$  cubic centimeters; plasma, blood,  $0.2 \times$  cubic centimeters.

†Enter in foods and beverages column all intake such as formula, tea, fruit juices, broth, but not glucose in water or saline.

‡Enter all glucose, whether administered orally or parenterally.

§Enter in saline value column the sum of: cubic centimeters of saline; cubic centimeters of glucose in saline;  $0.5 \times$  cubic centimeters of plasma, blood.

||Protein intake in grams,  $0.05 \times$  cubic centimeters of plasma, blood, amigen; also ingested protein.

It may be of interest to list the solutions used in the management of the patients. They included a 3.7 per cent solution of sodium bicarbonate or a one-sixth molar sodium lactate solution to correct acidosis; normal saline, 5 and 10 per cent solutions of glucose or glucose in saline, blood, plasma, and a 5 per cent casein hydrolysate solution in 10 per cent glucose\* to supply salts, fluids, calories, and nitrogen, and to restore and maintain circulatory volume.

A fairly simple fluid sheet, devised to provide a summary of the daily intake of the infant, is shown in Chart I. The house officer charts on this sheet each

\*The use of a closed system of fluid administration and rigid precautions against contamination were found necessary in the use of this solution, as it is an excellent culture medium for bacteria.

day the amounts of fluid, saline, calories, and protein the baby has received during the past twenty-four hours. In the first column is recorded in cubic centimeters the oral intake of foods and beverages; in the second, the cubic centimeters of sodium bicarbonate or lactate solution; in the third and fourth, the amount of glucose in water and in saline; in the fifth, the cubic centimeters of physiological saline (0.9 per cent); in the sixth, plasma and whole blood; and finally, casein hydrolysate solution. The last three columns are a summary of the intake for the day. For saline values the oral intake in the food is disregarded and only the amounts administered as normal saline, glucose in saline, and that included in blood and plasma are totaled. One-half the volume of blood and plasma is calculated as saline. The total protein includes the oral intake and that given as plasma, whole blood, and casein hydrolysate solution: for these three a protein concentration of 5 per cent is assumed. In the lower right half of the column the appropriate calories are entered. These are totaled and entered in the first column of the summary below the diagonal. After examining the patient and reviewing the record, the house officer is in a position to plan the fluid management for the next day.

#### CASE REPORTS

Charts II to XII are a graphic portrayal of experience based on this scheme. Nine represent cases of chronic diarrhea and two, cases of inability to ingest food. Supplemental saline, protein, calories, and total fluids are entered in separate rows. The days are shown in figures on the abscissa. The distance above the base line represents the total intake for the day. The oral intake is blocked off below in black, while the parenteral intake is represented by the white portion above. The figures nearest to the ordinates indicate the total amounts, the second set of figures to the left, the amounts per kilogram of body weight. A broken line has been drawn across each row to show the daily maintenance requirement for each child, calculated according to his body weight. The weight of the child is recorded at the top of the chart.

CASE 1—H. R., a 7 month old infant, had been ill for one week with high fever and a slight cough. The cough and fever continued for seven weeks after admission, although no cause for either was ever found. Five days after admission he developed a mild diarrhea, vomited, and refused food. Stool cultures were negative except for the presence of atypical colon bacilli. He lost 1.5 kg of weight in a period of two weeks. A period of temporary starvation with parenteral fluid therapy resulted in improvement, but diarrhea and vomiting recurred as soon as oral feedings were resumed. He became acidotic. The acidosis and dehydration were corrected with sodium bicarbonate and saline, and the long period of parenteral therapy shown in Chart II was begun. He was starved for two days, small feedings were tried for the next three days without success, and he was then starved for five days, with all food and fluid given parenterally. At the end of this time oral feeding was cautiously resumed while venoclysis was continued. There was no vomiting or increase in diarrhea on this occasion but the appetite was poor. As the diarrhea abated toward the end of the period he developed hypocalcemia and was therefore treated with calcium.

The fever and slight cough continued for four more weeks but diarrhea did not recur, the patient ate well and gained slowly. When seen for the last time at the age of one year he weighed 11 kg and was healthy and mentally alert.

This, the first experience with a long period of parenteral therapy, was undertaken before the adoption of a fluid summary sheet. One sees that too little saline and total fluid were given the majority of the time. The irregularity of protein intake is explained by the fact that the casein hydrolysate solution was

Chart II.

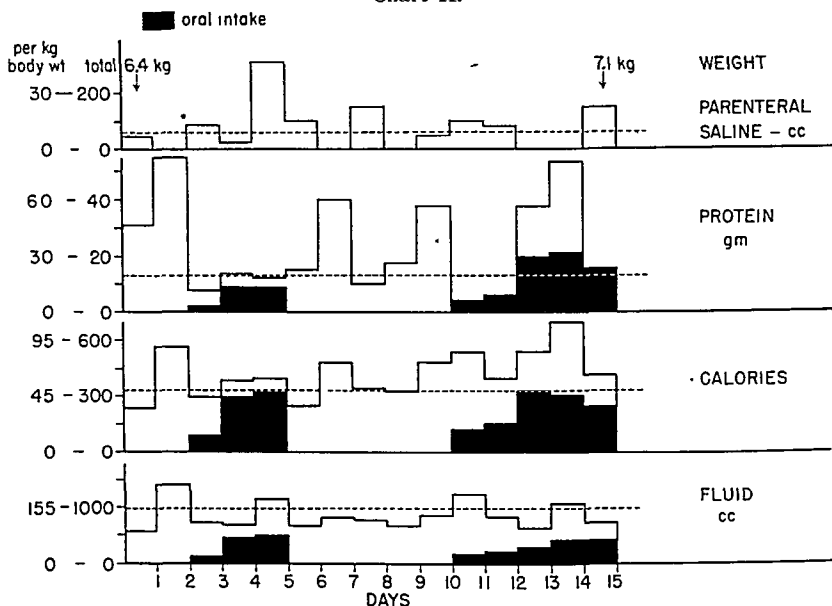
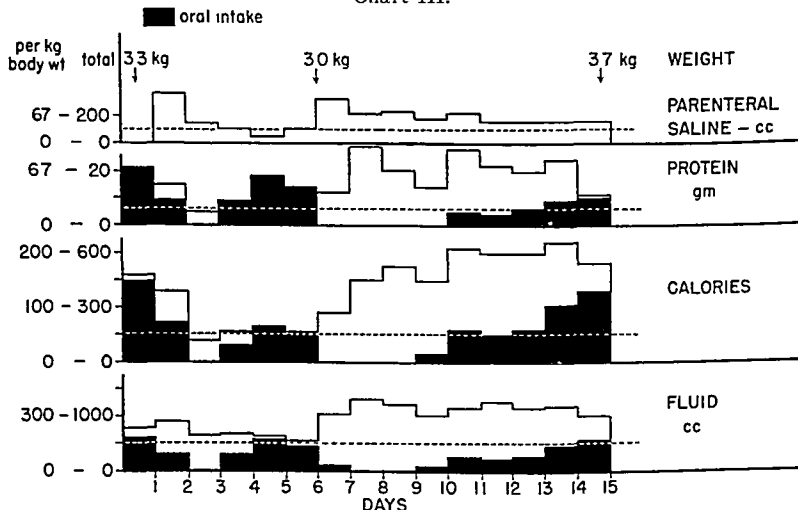


Chart III.

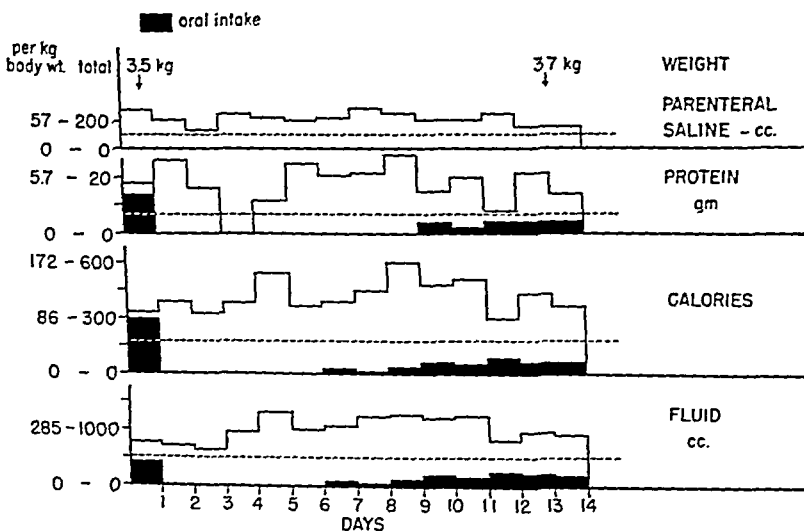


at this time supplied in one-liter bottles and that a whole flask was administered at one time. The patient's nonprotein nitrogen was elevated throughout the period, probably because of his low fluid intake and fever. He gained 0.7 kg. while on venoclysis.

CASE 2.—D. A., an infant 5 weeks of age, developed diarrhea and vomiting three days before admission. On admission he appeared undernourished and dehydrated. He weighed 0.3 kg. less than his birth weight. A short period of starvation and venoclysis was followed by ten days of moderate improvement, following which he again developed diarrhea and became dehydrated. Chart III begins with the last day of his oral feedings. A second two-day period of starvation with correction by saline and the administration of some plasma and glucose was followed by a second attempt at oral feeding which resulted in diarrhea, vomiting, and refusal of food, and led to dehydration and acidosis. These were corrected with saline and sodium bicarbonate solution, and the patient was maintained on venoclysis for nine more days with gradual resumption of oral feedings after four days. At the beginning of this last nine-day period he looked moribund and had hypocalcemia. Treatment with calcium, potassium, and phosphorus was given with apparent benefit. The stool culture at this time was positive for *Proteus morganii*. The patient gained 0.4 kilogram while on parenteral therapy. Thrombophlebitis occurred in both legs but fortunately healed well. The patient remained in the hospital one more month, during which time he suffered two slight relapses. He was discharged well.

The fluid and chloride intake were adequate and evenly distributed. The resumption of oral feedings while venoclysis is being continued has proved far more satisfactory in cases of chronic diarrhea than the abrupt cessation of venoclysis at the time when oral feeding is resumed. The failure of the first and second attempts at feeding and the success of the third illustrates this point.

Chart IV.

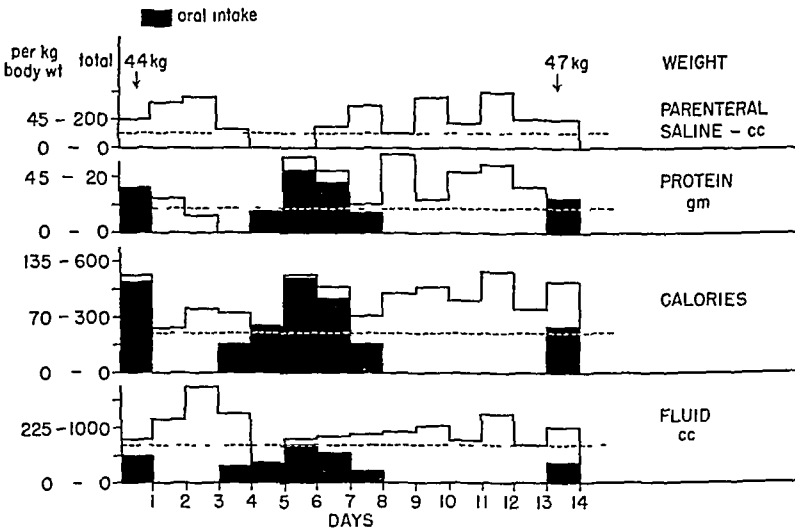


CASE 3.—G. A., a 2-month-old infant who had never eaten well since birth, began vomiting one week before admission. Five days later diarrhea commenced and on admission he weighed 0.5 kg. less than his birth weight. He was put on continuous venoclysis for eighty-four hours before his diarrhea stopped. It recurred with the resumption of oral feeding, and another period of thirty-six hours of parenteral therapy was given. Diarrhea, vomiting, and refusal of food recurred a second time when food was given. Chart IV starts with the last day of his oral feedings when his dehydration was corrected with saline. He was then maintained on venoclysis alone for five days, after which time food was started and gradually increased in amount. During this time diarrhea never ceased, although it lessened in severity.

*P. morganii* was cultured from the stools. The infant developed hypocalcemia and hypoprothrombinemia with hemorrhagic manifestations, for which conditions he was treated. At the end of the period he had a rise in temperature and became jaundiced. It was discovered that he had a large abscess at the site of the last venipuncture and septicemia, both caused by *Aerobacter aerogenes*. Surgery and streptomycin cleared up the infection. Unfortunately his subsequent course was marred by several complications unrelated to the parenteral therapy illustrated in the chart.

The management of the parenteral fluids appears on the whole satisfactory. The casein hydrolysate solution in use at this time did not contain any mercurial antiseptic (Merthiolate). Its contamination was undoubtedly responsible for the sepsis, since *A. aerogenes* was cultured from the casein hydrolysate solution itself.

Chart V.



CASE 4—C N, a 9 month old baby, had pertussis at 3 months of age and was admitted to another hospital at 7 months of age for diarrhea. His weight gain had never been sufficient. Diarrhea and vomiting started one week before admission. The stools were liquid and streaked with blood. Stool cultures were positive for *Shigella paradysenteriae* and *P. morganii*. He was treated with parenteral fluids and sulfadiazine and received a skimmed milk formula for nine days but lost his appetite and began to have almost continuous green liquid stools. Chart V starts with his last day on formula. His acidosis was corrected and he was put on exclusive venoclysis for three days, but when oral intake was resumed he vomited and the diarrhea grew worse. Venoclysis was started again. The child gained 0.3 kg. while on intravenous alimentation. Hypocalcemia developed as the diarrhea stopped. When feedings were resumed at the end of five days he did exceedingly well. Since discharge he has improved both physically and mentally.

This was a smooth-running clysis except for too early resumption of oral feeding at first.

CASE 5.—A. M, a 3 month old infant, had never done well. Diarrhea and vomiting began three days before admission. He was moderately dehydrated and markedly emacrated but only mildly acidotic. Chart VI begins with his admission. He was started on venoclysis and small amounts of oral feedings were begun on the second day. The clysis was discontinued

after three days, but the child refused most of his formula and vomited. After twenty-four hours the clysis was resumed for three more days while oral intake was gradually built up. He then showed steady improvement. All stool cultures were negative for pathogenic bacteria.

This represents a very smooth venoclysis in an emaciated child with caloric and protein intake adequate from the beginning. The only abnormal chemical finding was a decreased serum calcium after the diarrhea stopped.

Chart VI.

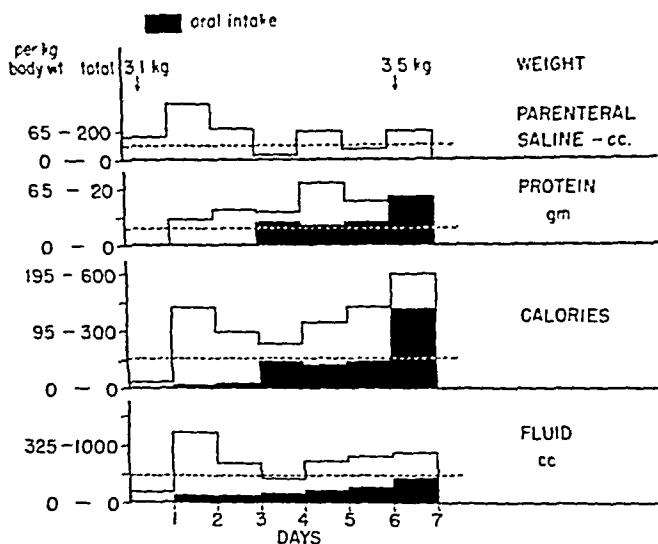
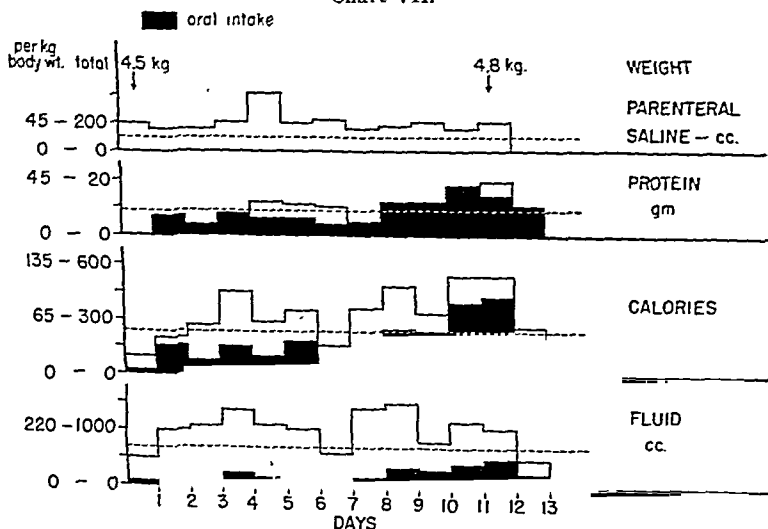


Chart VII.



CASE 6.—S. R., a 5-month-old infant admitted with a history of mild enteritis and vomiting, was treated with a short period of starvation and venoclysis and apparently recovered. One week later, fever, diarrhea, and vomiting recurred. Stool cultures were negative for pathogenic bacteria. Chart VII begins with the treatment of the relapse. She



was treated with venoclysis for thirteen days but oral feedings were never omitted. Her appetite was very poor for the first eight days and some vomiting occurred. Gradually the appetite improved but venoclysis was continued as the child still did not take sufficient food or fluid. She was never acidotic, but became hypocalcemic as the diarrhea ceased.

Chart VIII.

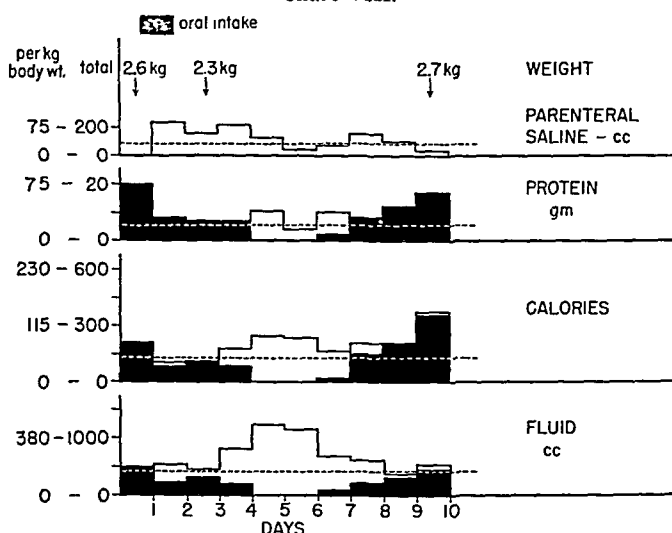
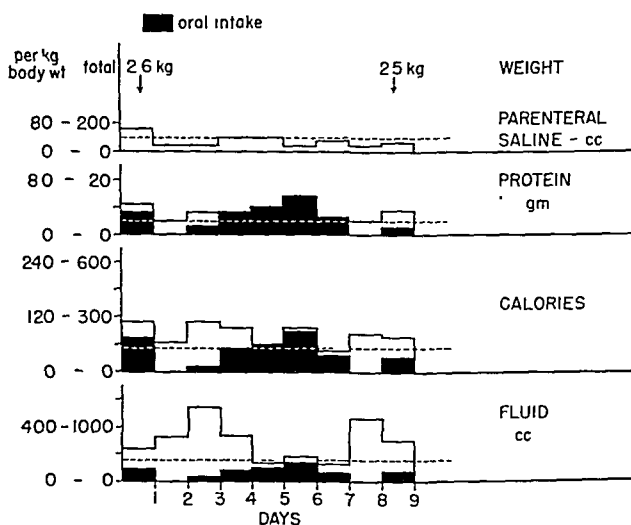


Chart IX.



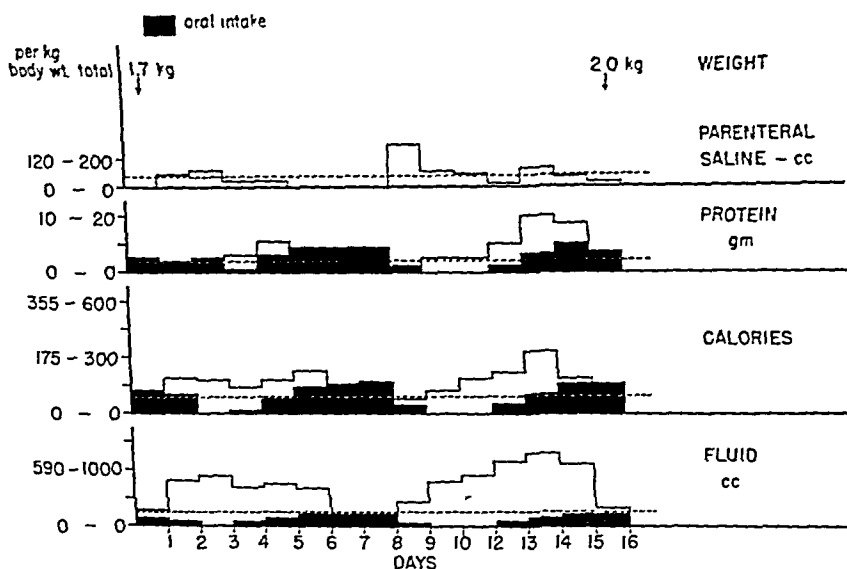
CASE 7.—D. G., a 7-week-old triplet who weighed 1.4 kg. at birth, had already had one or two bouts of diarrhea. He did well for two weeks after admission when diarrhea again developed. Stools were found positive for virus. Chart VIII starts at this point. Because of his small size, feedings supplemented by parenteral fluids were first tried. There was no abatement of the diarrhea, the child's appetite became worse, and vomiting occurred. He was starved for two days with all fluids given parenterally. Feedings were resumed and gradually increased while parenteral fluids were continued. Ten days after the commencement of parenteral fluid therapy he was doing well.

The serum chlorides were always high during his period of diarrhea with figures ranging from 127 to 135 milliequivalents per liter, and therefore little saline was given. The fluid intake exceeded 400 c.c. per kilogram in one twenty-four-hour period without any evidence of edema or other untoward results.

CASE S.—D. G., a second one of the triplets, who weighed 1.7 kg. at birth, had a similar history. His stools were also positive for virus. Chart IX begins with his first period of parenteral therapy. He required two periods of intravenous administration of fluids, after which he did well on oral feedings with occasional supplements.

At the beginning of therapy serum chlorides were 128 milliequivalents per liter. They rose at one time to 143 milliequivalents per liter. Fluid intake reached as high as 500 c.c. per kilogram of body weight in one twenty-four-hour period without ill effects. This case also illustrates the low saline requirements of premature and young infants with diarrhea.

Chart X.



CASE 9.—B. A., an 11-day-old premature infant who weighed 1.7 kg. at birth, was admitted to the hospital weighing the same as at birth. She developed diarrhea six days later and lost 0.2 kg. in three days. Stools were positive for virus. Chart X begins at this point. Oral feedings were continued, supplemented with parenteral fluids, but the diarrhea continued, she refused to eat, and became acidotic. The acidosis was corrected with bicarbonate solution and saline, oral feedings were discontinued for two days, and continuous venoclysis was instituted. Feedings were then resumed, but after four days she began to refuse her formula, her diarrhea increased, and she was again found to be acidotic. Her acidosis and dehydration were corrected again, and she was taken off food for two days. Feedings were gradually resumed while parenteral fluid administration continued. Her appetite remained poor for some time, so that it was fifteen days after the commencement of therapy before she could go on oral feeding alone. Her weight had risen to 2 kg. She had a brief relapse a week or more later but was discharged well after two months weighing 2.8 kg.

Serum chlorides were also high and therefore saline intake had to be kept low. Fluid intake reached a peak of 700 c.c. per kilogram of body weight in one twenty-four-hour period.

Chart XI.

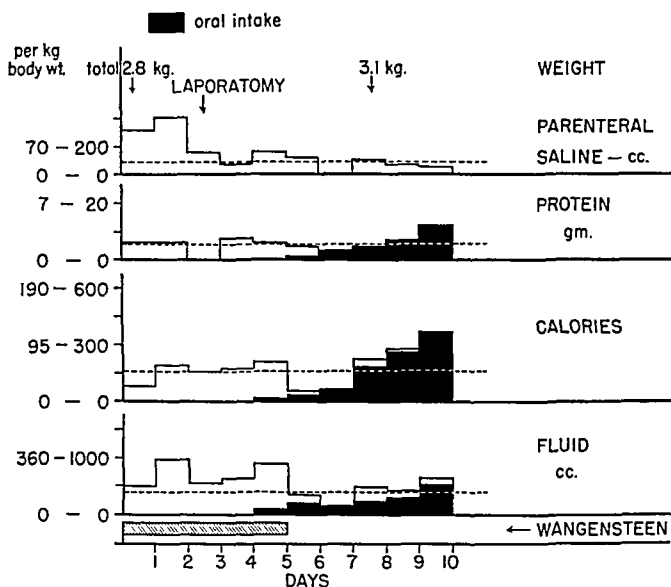
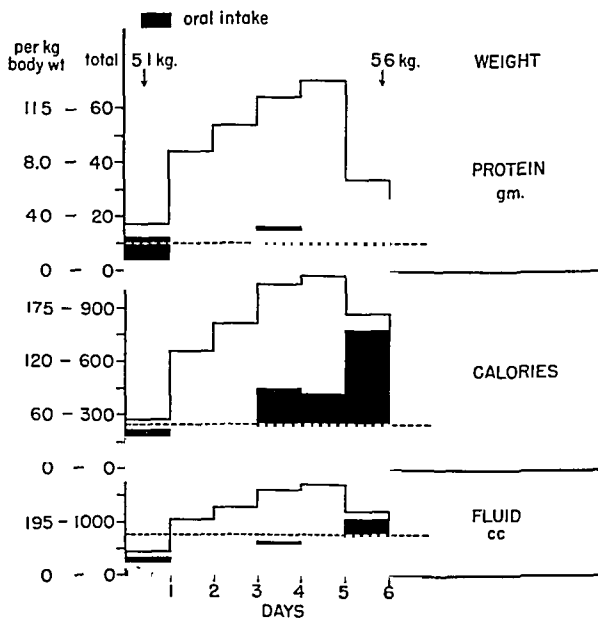


Chart XII.



The next two cases represent different indications for parenteral therapy.

CASE 10.—G. A., a newborn infant with a history of vomiting bile stained material for six days, was admitted to the hospital. She had received saline subcutaneously several times. On admission she had obviously lost weight. Her blood chemistry was not significantly abnormal so that the main problem was one of parenteral alimentation. Chart XI portrays her course in the hospital. She was fed by venoclysis for two days and then a laparotomy was performed. Malrotation of the gut with volvulus was found. After operation she was fed exclusively by vein for two more days, then small amounts of glucose water and later increasing amounts of formula were given. At the end of ten days she had gained 0.3 kg. and looked well.

In the first few days considerable amounts of intestinal contents were aspirated by Wangenstein drainage but little fluid was lost following laparotomy.

CASE 11.—B. V., a one-year-old child with celiac disease, was admitted to the hospital weighing 5.5 kg. After a slight initial weight gain he had a rise in temperature and lost 0.7 kg. in the next two weeks. He became so weak that he was unable to ingest sufficient food or fluid to maintain his hydration or his weight. Chart XII begins at the point where he was started on continuous venoclysis of 5 per cent casein hydrolysate in 10 per cent glucose solution, and was offered at the same time a milk substitute by mouth. In six days he regained 0.5 kg., and his appetite became excellent so that he was able to maintain a steady weight gain on oral feedings thereafter.

This case illustrates the supplementation of oral intake by parenteral fluid, nitrogen, and calories in a child too weak to ingest and digest sufficient food by mouth.

#### CONCLUSIONS

1. It has been shown that maintenance of fluid and electrolyte equilibrium by parenteral fluid administration is possible even in small infants during periods of partial or total withdrawal of oral feeding. With the use of glucose, whole blood, plasma, and casein hydrolysate, a gain in weight may be achieved.
2. A daily record of total intake of fluid, saline, calories, and nitrogen as part of a careful plan is an essential prerequisite of such a program.
3. Frequent observation of the clinical appearance of the infant and of his electrolyte and osmotic equilibrium is necessary.
4. Wide variation may be permitted in total fluid intake, provided salt intake is carefully regulated and is not excessive.
5. Premature and very young infants require less saline in proportion to their body weight than do older infants.
6. Contamination of the casein hydrolysate given, infection at the site of needle punctures, and thrombosis of the veins present a considerable problem. By the use of a closed system of administration, the more serious difficulties have been almost completely overcome. Thrombophlebitis and wound infection continue to be troublesome.

#### REFERENCES

1. Elman, R.: *Ann. Surg.* 112: 594, 1940.
2. Brunschwig, A., Clark, D. E., and Corbin, N.: *Ann. Surg.* 115: 1091, 1942.
3. Clark, D. E., and Brunschwig, A.: *Proc. Soc. Exper. Biol. & Med.* 49: 329, 1942.
4. Brunschwig, A., Bigelow, R. R., and Nichols, S.: *J. A. M. A.* 129: 441, 1945.
5. Hartmann, A. F., Lawler, H. J., Meeker, C. S.: *J. PEDIAT.* 24: 371, 1944.
6. Helfrick, F. W., and Abelson, N. M.: *J. PEDIAT.* 25: 400, 1944.
7. Butler, A. M., and Talbot, N. B.: *New England J. Med.* 231: 585, 1944.

## RETROLENTAL FIBROPLASIA

T. L. TERRY, M.D.

BOSTON, MASS.

**A**N OCULAR maldevelopment characterized by the presence of some of the branches of the hyaloid artery and tunica vasculosa lentis has long been recognized. It had been called persistence of tunica vasculosa lentis or fibro-vascular sheath, but these terms were misleading. It rarely occurred before extremely premature infants survived with any degree of frequency, and it sometimes involved only one eye in the full-term infant. Often the eye was needlessly removed following the erroneous diagnosis of retinoblastoma, a highly malignant tumor.

A research project to investigate this abnormality was motivated some six years ago by the examination of a patient with a bilateral ocular lesion. The history of extreme prematurity was outstanding. Search for other cases soon revealed that prematurity and the ocular abnormality, usually bilateral, were frequently associated. Since then, the study of this condition has become of major research interest in the Pathology Laboratory of the Massachusetts Eye and Ear Infirmary. From this study, several definite statements can be made.

The ocular lesion consists of:

1. A growth of embryonic connective tissue behind the crystalline lens.
2. The presence of only a few branches of the tunica vasculosa lentis carrying blood.
3. The presence of the hyaloid artery (seen in those cases where the retrolental mesenchyme does not cover the entire posterior surface of the lens).
4. An abnormally light-colored iris, usually blue, resulting from inadequate resolution of mesoderm on the anterior surface of the iris.
5. Retinal folds and even massive retinal separation which are found frequently enough, in instances where the fundus can be viewed in part, to be classed as a common primary finding.
6. Possible variations in severity from extensive involvement to minute traces which are commonly seen on the temporal side of the posterior lens surface.
7. Failure of the iris angle to differentiate.
8. Failure of any other part of the body to show abnormalities of a consistent type in association with the ocular abnormality, suggesting that the lesion is strictly a disturbance of the developing eye. One exception to this may be angiomas which are frequently in the skin. Reese<sup>1</sup> first recorded this. The fre-

<sup>1</sup>Presented at the meeting of Region I, American Academy of Pediatrics, New York, N. Y., April 1, 1946.

Because of the illness of Dr. Terry, this paper was presented by Dr. Paul M. Runge, First Assistant Ophthalmic Surgeon, Massachusetts Memorial Hospital, and Clinical Assistant, Massachusetts Eye and Ear Infirmary, Boston, Mass.

quency of angiomas in our series is some 17 per cent, but their occurrence in premature infants without retrolental fibroplasia does not appear to have been recorded. The original opinion that mental retardation was an associated and not infrequent finding has been disproved by the observation of three children who had been diagnosed as feeble-minded by experts. They have developed into individuals of unquestionably normal mentality under the guidance of preschool teachers skilled in working with the blind.

There are many changes which at the present time are considered to be sequelae or complications of the essential, abnormal, ocular development:

1. Lack or retardation in retinal development may be secondary when the abnormality is bilateral and a searching nystagmus is seen. Even when the lens is only partially covered, poor vision and macular differentiation are indicated by the searching nystagmus which is so frequently observed. The macula does not normally differentiate until some six months after full-term birth.

2. Early shallowing of the anterior chamber appears to be caused mechanically by contraction of the retrolental mesenchyme as it matures. Surgical removal of the lens restores the chamber. Later, the shallowing seems to result from a failure of aqueous humor to form in normal amounts.

3. Lentocorneal synechia often follow the obliteration of the anterior chamber.

4. Corneal opacities then develop in the region corresponding to the synechia.

5. There is failure of aqueous to form or to accumulate in normal amounts. Thus, the eye fails to grow.

6. Posterior synechiae and bound-down pupils develop.

7. Where some ability to form aqueous humor is retained, in perhaps 5 per cent of the cases, glaucoma occurs, but usually the eye coats are already strong enough to resist the stretching which would produce hydrophthalmos, a usual consequence of early and congenital or infantile glaucoma.

Any classifications such as Reese and Payne<sup>1</sup> have made, based on the severity of the involvement, should separate sequelae and complications from the essential features of the disease.

In the clinical study and the meager statistics available, the most striking association is that of retrolental fibroplasia with premature birth. Of the one hundred cases seen periodically, seventy-four are infants who weighed  $3\frac{1}{2}$  pounds or less at birth. Other observers seem to doubt that prematurity is even an exciting cause of the abnormality.<sup>1, 2, 3</sup> They appear to give no serious consideration to the fact that both Clifford<sup>4</sup> and I have seen this ocular abnormality develop in apparently normal eyes eight weeks or more after birth. We do not say that retrolental fibroplasia must invariably develop after birth, only that we have seen it develop in three cases. Again, the cause of prematurity varies in infants with retrolental fibroplasia, in similar proportions as the cause of prematurity in infants who do not develop the abnormality.

Thus, there is no common ground for the production of prematurity and production of the eye defect. Their relationship, however, is so frequent that it must be explained.

Recently, Bakwin,<sup>5</sup> in discussing a paper by Sitchevska analyzing all cases available from the literature, stressed the ratio of males to females as eight to five. If the ratio is maintained, could it mean that absence of ovarian hormones, even those from the premature female ovary, is a stimulating factor, or perhaps that the presence of male sex hormones, even from the premature testicles, favors retrolental fibroplasia formation? Of course, such a question is an exercise in considering and weighing all conceivable etiologic factors. Although we think of such questions, and may even give expression to them, we do so with considerable mental reservation.

Bakwin also points out the apparent lack of parallelism in frequency of retrolental fibroplasia and the increasing survival rate of the premature infant. This is, indeed, worthy of further consideration. All of us will agree that we do not have a sufficient number of cases for us to feel sure that our present statistics are of proved value. I am still puzzled over the apparent variations in the frequency of retrolental fibroplasia in different medical centers. Proof that there is a variation is lacking, but there are strong suggestions that such a variation does exist. Some individual differences in technique of premature infant care in these centers may act as at least an exciting etiologic factor.

None of the various classes of etiologies can be absolutely excluded. These include heredity, those causes operating before birth, those arising through premature separation from maternal hormones, the precocious functioning of systems such as the respiratory, digestive, and cardiovascular, the heat regulatory center, and those arising through precocious exposure to light. It appears that a common exciting factor is related to premature birth and incubator life. It seems logical that, of the etiologies limited to the eyes alone, precocious exposure to light is still the leading factor in the cause of ocular developmental abnormalities, yet no clinical or experimental finding strongly supports this. Heredity seems least likely. To know whether we are studying one disease entity or several which have similar clinical features but different causes would more clearly define our problem.

The value of treatment from the ophthalmologist is relatively meager. We have no cure. We do have medical and surgical treatments aimed at prevention or eradication of complications.

The greatest value, however, is to be derived from social service workers and preschool teachers. The social service worker first helps the parents to overcome their emotional sense of guilt and frustration and then provides suggestions and resources available to make a good citizen of the blind child. The preschool teacher for the blind aids the parents in teaching their child to chew solid food, to dress himself, and then to appreciate the nature of the world about him.

This ocular abnormality is still one of the great challenges in relation to prematurity. The prognosis at best is questionable, but until it is proved to be

hopeless, we have no right to abandon all efforts at treatment. To have a really close relationship between the pediatrician and the ophthalmologist, not only in routine clinical studies, but also in experimental and investigative research, would speed the solution in a mutually advantageous manner.

## REFERENCES

1. Reese, A. B., and Payne, F.: *Persistence and Hyperplasia of the Primary Vitreous (Tunica Vasculosa Lentis or Retrolental Fibroplasia)*, *Am. J. Ophth.* 29: 1, 1946.
2. Krause, Arlington C.: *Congenital Encephalo-ophthalmic Dysplasia of Unknown Etiology*, *Arch. Ophth.* In press.
3. Mann, Ida C.: Personal communication. Discussion of Reese and Payne paper.<sup>1</sup>
4. Clifford, S.: Personal communication.
5. Bakwin, R.: *Retrolental Fibroplasia: Discussion of Dr. Olga Sitchevska's Paper*, Presented at the Ophthalmological Section of the Academy of Medicine, New York, N. Y., Feb. 18, 1946.



# MUCOUS CYST AT BASE OF TONGUE AS A CAUSE OF SUDDEN DEATH IN AN INFANT

## REPORT OF A CASE

LA MONT WHITTIER, M.D., AND EDWARD F. DOMBROWSKY, M.D.  
ANCON, CANAL ZONE

**A**LTHOUGH mucous cysts of the lips, cheeks, and lower surface of the tongue are not uncommon, the literature contains relatively few reports of such cysts located at the base of the tongue. Because of the presence of numerous glands in this area, as well as the complex embryological development of the tongue, one would expect to see such lesions more frequently. Cysts at the base of the tongue may originate either from incomplete obliteration of the lingual portion of the thyroglossal duct, or from mucous glands. The former are usually found in the midline beneath the foramen caecum.<sup>1</sup> They are lined by stratified squamous or ciliated epithelium. Mucous or retention cysts occur when the mucous glands in this area become obstructed. Such cysts are usually located between the epiglottis and the foramen caecum, and may be either in the midline or lateral to it.<sup>1</sup> Reimann<sup>2</sup> suggests that mucous cysts in this area may originate from the efferent tubules which accompany the thyroglossal duct.

Thyroglossal cysts are rarely present at birth, but generally form between the third week and the thirty-first year of life.<sup>3</sup> Mucous retention cysts at the base of the tongue have been described most often in infants. In this location they may become large enough to produce laryngeal stridor and asphyxia.<sup>1</sup>

The purpose of presenting this case is not to point out a rare lesion but rather to emphasize that a large mucous cyst at the base of the tongue can cause asphyxia and death.

## CASE REPORT

A 2-month-old Panamanian mestizo male was admitted because of difficulty in breathing. The parents stated that the baby had appeared to breathe with more or less difficulty ever since he came home from the hospital after a normal delivery. The respiratory difficulty had become worse previous to admission. Physical examination revealed a well-nourished and hydrated male infant with mild inspiratory difficulty and with evidence of a mild upper respiratory infection. The temperature was 99.2° F. Laboratory procedures, including blood calcium and phosphorus, and x-ray of the chest, revealed nothing abnormal.

Mild inspiratory stridor was noted only at times when the baby was lying on his back. This would disappear when the baby was turned onto his abdomen. He took his feedings well with no vomiting. He was discharged with the diagnoses of rhinopharyngitis, acute catarrhal otitis media, and congenital laryngeal stridor.

Eight days later the baby was readmitted to the hospital with the complaints of refusal to eat and of coughing, choking, and vomiting when the formula was forced. He was dehydrated and had lost one pound in the interval between admissions. The temperature was 100.8° F. There were musical râles over the left lung. Findings from routine laboratory examinations were within normal limits.

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From the Pediatric Service and The Board of Health Laboratory, Gorgas Hospital.

The baby took his feedings with reluctance, often choking and sometimes vomiting when they were forced. He also vomited frequently following feedings. Transient cyanosis often appeared when he choked or vomited. Because of the vomiting, repeated clyses were necessary to maintain hydration. Three days after admission, the infant had been given his formula with considerable difficulty and had several spells of transient cyanosis. Shortly after this feeding he was found to be extremely cyanosed. Breathing had stopped. Vomitus was noted about the mouth and neck. The heart was beating feebly but soon ceased despite artificial respiration and stimulants. Esophageal-tracheal fistula, achalasia of the esophagus or possibly some form of congenital laryngeal stridor were among the diagnoses entertained prior to death.

**Gross Autopsy Observations.**—A complete autopsy was performed three and one-half hours after death. No abnormalities were noted in any structures other than the tongue.

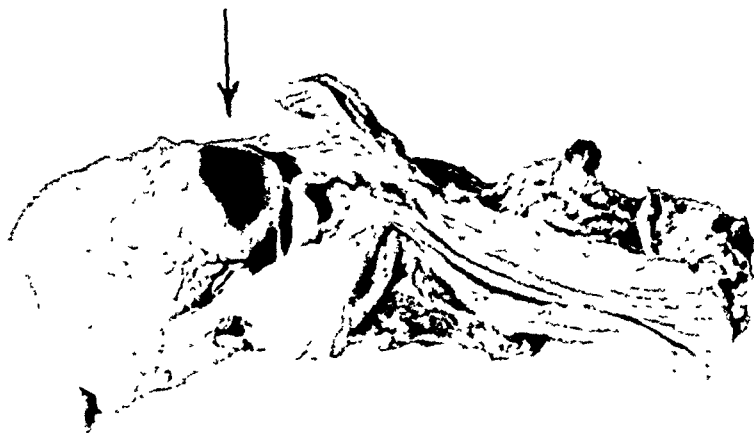


Fig. 1.—In the photograph the arching dome of the cyst appears depressed, but this is probably due to postmortem discoloration. However, the size and position in relation to the epiglottis are illustrated nicely. Note the raphe connecting the cyst to the epiglottis.

**Tongue:** At the base of the tongue and slightly to the right of the midline, a bluish-gray, thin walled cyst was observed. This cyst was circular, protruded 1.5 cm. from the superior surface of the tongue, extended 1.0 cm. into the substance of the tongue, and measured 2.5 cm. in diameter. The posterior margin of the cyst was located 0.2 cm. anterior to the base of the epiglottis and was attached to it by a thin membranous raphe. Lifting the tongue or pushing it slightly posteriorly caused the cyst to press against the epiglottis, completely closing the laryngeal orifice. This obviously was the mechanism which caused asphyxia and death in this patient. The cyst was filled with a thick, clear, mucoid material. The lining of the cyst was smooth and pale gray.

**Microscopic Examination.**—The dome of the cyst wall consisted of three distinct layers. The outermost zone was composed of a narrow layer of atrophic surface squamous epithelium. The central and thickest layer consisted mainly of compressed muscle fibers and a few scattered zones of flattened mucous glands. The lining of the cyst wall was composed of a layer of cuboidal to low columnar cells varying from one to two cells in thickness. Sections stained with mucicarmine revealed the glands within the muscular layer and the cells lining the cyst to be mucous in type. The cyst contents showed similar staining characteristics.

#### DISCUSSION

As stated by Holt and McIntosh,<sup>4</sup> "sudden death is not a very uncommon occurrence in infants who are apparently healthy or appear to be suffering

only from some minor ailment." Asphyxia is among the more frequent of the conditions listed as possible causes of sudden death. This may result from the aspiration of food, mucous, or foreign bodies. Abramson<sup>5</sup> gives prominence to accidental mechanical suffocation as a cause of death in infants. Woolley<sup>6</sup> questions the frequency with which the diagnosis of suffocation due to bedding, sleeping attire, or other mechanical means is made. He believes that careful autopsies in all such cases would often reveal other causes such as overwhelming infections and congenital anomalies.

Although uncommon, a mucous retention cyst at the base of the tongue should also be considered in the differential diagnosis of asphyxia. Whenever unexplained choking, dyspnea, or cyanosis occurs in an infant, a cyst of this nature should be ruled out by careful visualization of the base of the tongue. The importance of this becomes more apparent when it is realized that this condition is readily amenable to treatment. Since these cysts are usually near the midline, the ordinary large wooden tongue depressor may cover and flatten them, obscuring them from the examiner. A small infant size tongue blade should therefore be used in this examination.

#### SUMMARY

1. A case of sudden death due to a mucous retention cyst at the base of the tongue is reported.
2. Though uncommon, cysts in this area must be considered in the differential diagnosis of asphyxia in infants.
3. Cysts at the base of the tongue may be easily overlooked in the routine examination of the buccal cavity when the ordinary large wooden tongue depressor is used.

#### REFERENCES

1. Duncan, G. W., and Danile, R. A., Jr.: Cystic Tumor of the Tongue: Report of an Unusual Case, *Arch. Surg.* 44: 164, 1942.
2. Reimann, S. P.: *Pathology for Students and Practitioners*, ed. 8, Philadelphia, 1929, P. B. Blakiston's Son and Co., vol. 1, p. 507.
3. Thoma, K. H.: *Oral Pathology*, ed. 1, St. Louis, 1941, The C. V. Mosby Company, p. 273.
4. Holt, L. E., Jr., and McIntosh, R.: *Diseases of Infancy and Childhood*, ed. 2, New York, 1940, D. Appleton-Century Co., p. 60.
5. Abramson, J.: Accidental Mechanical Suffocation in Infants, *J. PEDIAT.* 25: 404, 1944.
6. Woolley, P. V., Jr.: Mechanical Suffocation During Infancy, *J. PEDIAT.* 26: 572, 1945.

# The Academy Study of Child Health Services

## REPORT OF THE COMMITTEE FOR THE STUDY OF CHILD HEALTH SERVICES

Less than one year ago, when the Committee for the Study of Child Health Services made its annual report in Detroit, this Academy study was just getting under way. The organization had been planned, a pilot study had been done, and financial support solicited. At that time, however, assets were measured in terms of optimism rather than cold reality. The Academy had committed itself to a nationwide study of child health services, but the members had little appreciation of the magnitude of the task or the fact that every individual member had a job to do if the project were to be successful. Today, ten months later, the Academy is well along the road toward a goal that increases in significance as it is approached.

### STATE STUDIES

First, a glance at the state programs: This is the most remarkable phase of our progress, and the credit is due to state chairmen together with their executive secretaries and advisory committees appointed for the purpose. Less than a year ago they were confronted by difficulties which appeared insurmountable. Today these difficulties have been met. The Study has been launched in all but two states in the country, including the District of Columbia and the Territory of Hawaii. The remaining two states are expected to start soon. In four states and the District of Columbia, the collection of data is complete, or nearly so, and the schedules sent in to the central office for analysis and tabulation. It is expected that all states will complete this phase of the study during the next few months. Despite earlier misgivings as to finding suitably qualified, full-time executive secretaries to assist state chairmen, they appeared when the importance of the Academy's venture began to be appreciated. A total of fifty-seven full-time, paid, executive secretaries have been engaged in the study throughout the country; of these, twenty-nine are pediatricians, the remainder coming from a variety of medical and sociological backgrounds. A year ago the office of State Chairman had no treasury or financial responsibility. However, state chairmen have financed their state programs to a collective total of approximately \$450,000.

### REPORTING THE STUDY

At the outset it was assumed by the Committee for the Study of Child Health Services and its director that their duties would be fulfilled in recording the factual data in one, overall report for the country as a whole. It now appears that this is only a part of the job. Recently, as the interest of local groups has grown, state chairmen have repeatedly requested the Executive Staff to return to them statistical data in sufficient detail to serve as a basis for reports for their own states. Consequently, in reporting the Study, the emphasis shifted from the national level to state, county, and local levels. This is a thoroughly wholesome development and has been willingly accepted by the Executive Staff despite the fact that it has increased the work far beyond that which was originally anticipated.

In planning the statistical tabulations for the state reports, it became apparent that there was an urgent need for members of the Executive Staff to meet with state chairmen in order to provide opportunity for a free interchange of opinions and to define in specific terms the amount and type of material to be returned to the states. For this purpose, three regional meetings were held during September in Chicago, San Francisco, and Washington. These meetings have been described in some detail in recent issues of THE JOURNAL. They were all

To have been presented at the annual meeting in Pittsburgh in November, 1946, which was cancelled.

well attended, clarified many problems, and gave significant impetus to the preparation of state reports. During the last of these three regional conferences held in Washington September 30 and October 1, there was a meeting of the committee, at which the discussion was chiefly concerned with establishing methods to assure that the information gathered during the study would be adequately and promptly reported at the state level as well as the national level. As a result of this discussion, the committee wishes to present to the Executive Board certain recommendations. At the state level these recommendations are intended to provide state chairmen a suitable opportunity to report the information before it is released to anyone else. At the national level the committee considers that its assignment will have been fulfilled when the data are duly recorded in a factual report, a report which should stop with a presentation of facts and should not attempt to make recommendations arising from those facts. *But* the committee is naturally anxious that this study into which has been poured so much time, effort, and money, should be put to proper use. Therefore, a further recommendation deals with the formation of a committee charged with the responsibility of implementing the study and translating it into an action program to accomplish the Academy's goal of improved health services for children.

#### STATISTICAL ANALYSIS

The preparation of detailed and tabulated material for forty-eight states, the District of Columbia and the Territory of Hawaii means a volume of work far beyond that which was originally planned. The statistical analysis that is now under way is such that it would take one man 100 years to complete. The Study Staff has been told to complete it by the end of next year, fourteen months from present date. Rather than having one poor soul growing old in the cause, a statistical team of fifty or maybe more is being developed to finish the job in the allotted time. The Academy is fortunate in having secured the services of Mr. Rollo Britten to act as chief of this statistical team. Having retired from the U. S. Public Health Service, he is now employed on a full-time basis by the Academy.

#### CENTRAL OFFICE

A year ago the central office of the study was in a small room of about seventy square feet made available through the kindness of Dr. Wall and the Children's Hospital in Washington. This room was barely large enough to accommodate the director and half a secretary; the other half sat in the hall. In February, 1946, when the Study was really under way, the office had to expand but there were insufficient funds for office rent. Therefore, the Director accepted a generous offer from the Surgeon General to occupy offices without charge in the Bethesda buildings of the U. S. Public Health Service. The staff is still in these offices, but again more space is needed to accommodate the large statistical force described above. In contrast to the seventy square feet of a year ago, some 6,000 to 8,000 square feet are now needed. It is not only more appropriate but indeed necessary to establish the office in downtown Washington, but it has been almost impossible to find suitable space for a short-term lease at a figure less than astronomical. Recently, with the approval of the Committee Chairman, the director requested and received from the President of the Academy, authority to sign a lease for rental of property at 2346 Massachusetts Avenue, NW, where, being a residential district, the rate for office space is about half that of the downtown area. Permission to establish an office at this location is now awaiting action by the Board of Zoning Adjustment of the District of Columbia. It would be appropriate for the Executive Board to confirm the authority given by the President to the Director to sign this lease or, failing favorable action from the zoning board, to sign a lease for other property at rates within the budget allowance.

#### STUDY OF PEDIATRIC EDUCATION

During the coming winter, as the collection of information from the states is completed, the Study of Pediatric Education, the second major part of the Academy Study will be developed. For this purpose a subcommittee has been formed consisting of Dr. James L. Wilson, Chairman, and six additional professors of pediatrics as follows: Drs. Henry Poncher, Samuel Levine, Waldo Nelson, Robert Lawson, Ralph Platou, and Francis Scott Smyth. Each has agreed to direct and participate in the Study in approximately ten medical schools in his

section of the country, thus covering all sixty-eight schools in the United States. The schools for which each is responsible were listed in the October issue of *THE JOURNAL*. A preliminary meeting of this committee was held in Washington, D. C., in June of this year at which time the first draft of the questionnaire schedules for this portion of the study (Series IV) and the general plan of action were discussed. Dr. John Mitchell, who, up to November 1, was director of the state program for Pennsylvania, is now director of this phase of the study. He, together with Dr. Hubbard, worked out a tentative schedule allowing one month to visit the medical schools in each of the seven areas during the current academic year. At the beginning of the month's visit to each area, the committee member responsible for that area will call a meeting of the chiefs of the pediatric departments of the schools assigned to him. Then, insofar as circumstances allow, the committee member will visit each school together with Dr. Mitchell or Dr. Hubbard. In this way the study of each school should include the opinions of an outstanding teacher of pediatrics plus those of a member of the Executive Staff whose past experience includes both teaching and practice and whose function will be to assure that in each school the same techniques of gathering information are used. Thus a consistent and most interesting picture of pediatric education should be obtained.

#### FINANCIAL REPORT

Finally a report on the financial status. On Jan. 25, 1946, Dr. Grulee turned over to the Director of the Study \$11,525.84. That's all there was except hope. Today the budget exceeds \$1,000,000. As mentioned above, nearly half of this is the collective total cost of state programs which has been met, not without considerable difficulty by state chairmen from sources within their own states including county chapters of the National Foundation for Infantile Paralysis, state health departments, medical and pediatric societies, contributions of individual pediatricians, local grants, and other local sources.

The finances of the Central Office of the Study are being administered by the Director through three separate accounts.

1. The first account designated as the "Foundation Account" was set up to administer a two-year grant of \$116,000 from the National Foundation for Infantile Paralysis. On April 5, 1946, \$67,500 was received in accordance with the budget submitted for the first year. The balance, \$48,500, is due April 1, 1947.

2. The second account, designated as the "National Institute of Health Account," was opened in November to administer a grant to the Academy from the National Institute of Health of the U. S. Public Health Service. This grant is intended to cover the cost of statistical analysis from Oct. 1, 1946, including salaries, office rent, machine rental, office equipment, and supplies for the statistical division. It will be recalled that in the early planning of the study, the committee requested the cooperation of the U. S. Public Health Service and the U. S. Children's Bureau. Both government agencies responded wholeheartedly; the Surgeon General offered to support the Academy in the technical and statistical aspects of the study in which the Academy had neither the necessary experience, personnel, nor equipment. As of recent date when it was possible to estimate the amount of work to be done by the statistical division, the director in the name of the Academy submitted to the Surgeon General a request for a grant-in-aid from the National Institute of Health based on a budget of \$249,750 to meet the further expenses of this division. As shown in the attached statement this request was made for the period Oct. 1, 1946, to Dec. 31, 1947, broken into two parts: \$128,550 for nine months from Oct. 1, 1946, to June 30, 1947, and \$121,200 for six months from July 1, 1947, to Dec. 31, 1947. The latter amount was considered subject to revision in the light of experience gained by next summer. After due consideration by the National Advisory Health Council the amount requested for the first term was approved in full, with assurance given that further support would be forthcoming to complete the study.

3. The third account which actually was the first one opened is designated as the "Academy Account." Into this account have been placed receipts from all other sources, including the reserve fund of the Academy itself, a grant from the Field Foundation, the New England Pediatric Society, and contributions from pharmaceutical and commercial houses. These receipts together with the expenditures from this account are also shown in the attached statement.

If to the receipts in these three accounts is added the total of estimated state budgets and an estimate of the value of services rendered by the U. S. Public Health Service and the U. S. Children's Bureau, a grand total somewhat in excess of \$1,000,000 is shown as the anticipated cost of the Study of Child Health Services.

#### THE NEXT STEP

The Academy may look with justifiable pride at having planned, organized, and successfully brought to the halfway mark a nationwide study of child health services. It may look with pride, not unmingled with awe, at having been able to call forth over \$1,000,000 to finance this study. It may look with pride at the publicity which its declared objectives have received throughout the country in professional journals and the lay press. However, this committee wishes to express its realization that success breeds responsibility and that unless the Academy makes full use of the interest which it has aroused and the information which it has collected, it will be blamed for a dismal failure. There is no thought that the Academy will fail, but it is felt that more attention must be given *now* to the next step. How are the results of this fact-finding study to be translated into an action program? What sort of a committee should draw up and implement recommendations arising from the facts? How, in short, is the Academy going to move closer toward its goal of planning for better and more evenly distributed health services for children? These questions should be a major concern of the Academy at this meeting.

Respectfully submitted,

JOHN P. HUBBARD, Director  
WARREN R. SISSON, Chairman  
ALLAN M. BUTLER  
HARVEY F. GARRISON  
HENRY F. HELMHOLZ  
LEE FORREST HILL  
JOSEPH I. LINDE  
ARTHUR H. LONDON, JR.  
JOSEPH S. WALL  
JAMES L. WILSON

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#### CERTIFICATE OF THE AUDITOR

November 6, 1946

To the Executive Board  
American Academy of Pediatrics  
Evanston, Illinois  
Gentlemen:

I have made an examination of the financial accounts and records of the American Academy of Pediatrics, Study of Child Health Services for the period from the opening of the accounts in February, 1946, to Oct. 31, 1946.

Without making a detailed audit of all transactions, I have satisfied myself that all recorded cash receipts were deposited in banks, and I examined cancelled checks and vouchers for the greater part of the disbursements. The bank balances have been verified by certificates from the bank. Accounting records and other supporting evidence have been examined by methods and to the extent I deemed appropriate.

In my opinion the accompanying statements of receipts and disbursements and reconciliation of accounts present fairly the financial conditions of the Study of Child Health Services at Oct. 31, 1946, and the results of its operations for the period under review, in conformity with generally accepted accounting principles.

Very truly yours,

MAX R. BYERS  
Certified Public Accountant

Washington, D. C.

## STATEMENT OF RECEIPTS AND DISBURSEMENTS, FEB. 1, 1946, TO OCT. 31, 1946

*Receipts:*

Restricted contributions:		
National Foundation of Infantile Paralysis	\$67,500.00	
Unrestricted contributions:		
American Academy of Pediatrics	16,022.16	
Mead Johnson & Company	15,503.68	
M & R Dietetic Laboratories Incorporated	10,000.00	
Carnation Company	10,000.00	
Pet Milk Company	10,000.00	
New England Pediatric Society	500.00	
Lederle Laboratories	5,000.00	
Field Foundation	5,000.00	
Cutter Laboratories	500.00	
<i>Total Receipts</i>		\$140,025.84

*Disbursements:*

Salaries (17 persons)	\$37,460.36	
Travel	9,966.60*	
Office equipment	2,865.48	
Postage	1,962.78	
Office supplies	1,716.70	
Printing and publicity	6,983.30	
Miscellaneous	50.65	
Telephone and telegraph	987.72	
State programs	16,870.02	
Periodicals and books	35.15	
Social security taxes	53.84†	
Car purchase, upkeep, and travel by car	2,643.81	
Premium on bonds	187.50	
Addressing and mailing	1,203.25	
Educational study	806.93	
<i>Total Disbursements</i>		\$3,794.09

*Balance:*

\$ 56,231.75

*Exhibit "A"*

## STATEMENT SHOWING RECONCILIATION OF ACCOUNTS, OCT. 31, 1946

Cash in bank—Foundation account	\$ 25,160.10
Cash in bank—Academy account	31,896.20
<i>Total Cash in Bank</i>	\$ 57,056.30
Balance available for expenditure, Exhibit A	\$ 56,231.75
Income taxes withheld from salaries	764.30
Social Security taxes deducted from salaries	60.25†
<i>Total</i>	\$ 57,056.30

*Exhibit "B"*

## COMMENTS

Receipts from the National Foundation for Infantile Paralysis are maintained in a separate bank account designated as the "Foundation Account." Disbursement of these funds is restricted within certain budget limitations. Separate accounting records are kept for receipts and disbursements from this "Foundation Account." The unrestricted funds are deposited in what has been designated as the "Academy Account." A proper record of these receipts and their disbursement is maintained. For the purpose of the accompanying statements the accounts have been consolidated.

\*Includes travel expense for regional meetings and for committee and field staff.  
†Subject to refund pending legislative ruling.



From the following source of funds received by the American Academy of Pediatrics during 1945 and 1946:

American Academy of Pediatrics Reserve Fund		\$18,000.00
Mead Johnson & Company	\$18,000.00	
the following amounts were expended for preliminary study from March, 1945, to February, 1946	2,496.32	1,977.84
	<u>\$15,503.68</u>	<u>\$16,022.16</u>

In order to cover further expenses of the statistical division application was made on Aug. 7, 1946, for a grant of \$128,550 from the National Institute of Health of the U. S. Public Health Service for the period Oct. 1, 1946, to June 30, 1947, with an additional \$121,200 for the period July 1, 1947, to Dec. 31, 1947; the latter amount being subject to revision in light of experience gained by July 1, 1947. This grant has been approved and a check in the amount of \$128,550 was received Nov. 1, 1946, expenditures from which may be retroactive to Oct. 1, 1946.

Following is a list of funds pledged to the American Academy of Pediatrics, Study of Child Health Services for receipt in 1947:

National Foundation for Infantile Paralysis	\$48,500
Field Foundation	5,000
Mead Johnson & Company	10,000
M & R Dietetic Laboratories, Inc.	10,000
Pet Milk Company	10,000
Carnation Company	10,000
Total pledged for 1947	<u>\$93,500</u>

Figures were not available at this time for the value of services rendered from July 31, 1946, to Oct. 31, 1946, by the U. S. Public Health Service and the U. S. Children's Bureau, but the following were set forth at a previous writing as of July 31, 1946:

Value of services rendered from July 1, 1945, to July 31, 1946, by:

U. S. Public Health Service	\$26,587
U. S. Children's Bureau	10,260
Total	<u>\$36,847</u>

Value of *anticipated* services rendered from Aug. 1, 1946, through Dec. 31, 1947:

U. S. Public Health Service	\$47,600
U. S. Children's Bureau	17,000
Total	<u>\$64,600</u>

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#### Addendum

In the report on the Academy Study of Child Health Services last month, The Albany Medical College, Albany, N. Y., and University of Vermont College of Medicine, Burlington, Vermont, which were assigned to Dr. Samuel Z. Levine, were inadvertently omitted.

# The Social Aspects of Medicine

## COMMUNICATION

### SUMMARY REPORT OF MEETING OF MATERNAL AND CHILD HEALTH ADVISORY COMMITTEE AND CRIPPLED CHILDREN ADVISORY COMMITTEE U. S. CHILDREN'S BUREAU, WASHINGTON, D. C. SEPTEMBER 16 and 17, 1946

On Aug. 10, 1946, Congress passed legislation amending Title V of the Federal Social Security Act, increasing the amounts authorized for annual appropriation to be used as grant-in-aid to the States as follows:

- A. Funds for Maternal and Child Health Services increased from \$5,820,000 to \$11,000,000.
- B. Funds for Crippled Children's Services increased from \$3,870,000 to \$7,500,000.
- C. Funds for Child Welfare Services increased from \$1,510,000 to \$3,500,000.

The Children's Bureau called the meeting of the Maternal and Child Health and Crippled Children Advisory Committees on September 16 and 17 at Washington, D. C., to confer upon matters relating to the extension and improvement of health services for mothers and children.

Dr. Oscar Miller, orthopedic surgeon, Charlotte, North Carolina, and Dr. Nicholson Eastman, Professor of Obstetrics, Johns Hopkins University, Baltimore, Maryland, served as co-chairmen of the Committees. Sixty-three of the seventy members of the Maternal and Child Health and Crippled Children Advisory Committees attended the meeting. Thirteen, invited guests from the fields of medicine, dentistry, nursing, and medical social work also attended.

This was the first meeting of the Advisory Committees held since the transfer of the Children's Bureau from the United States Department of Labor to the Federal Security Agency. Mr. Watson B. Miller, Federal Security Administrator, greeted the members of the Advisory Committees and guests at the opening session, and expressed his deep interest and concern in the development of improved health services for mothers and children in all sections of the United States. Mr. Miller stated that he had been acquainted with the work of the Children's Bureau over a period of years and believed that there should continue to be such a unit in the Federal Government which concerns itself solely with the health and welfare of mothers and children, and that he had no intention of dismembering the Bureau and scattering it among the other offices within the Federal Security Agency. He indicated, however, that many mutual benefits would be derived by having the Children's Bureau as an integral part of the Federal Security Agency working in close association with the numerous other units concerned with the fields of health, welfare, and education.

Mr. Arthur J. Altmeyer, Commissioner for Social Security, Federal Security Agency, spoke briefly before the conference and explained the position of the Children's Bureau in the Social Security Administration. He commented upon the social philosophy underlying the Social Security program and referred to the important role played by the Children's Bureau in the development of health and welfare services for mothers and children. Mr. Altmeyer reaffirmed the position taken by Mr. Miller in maintaining the integrity of the Children's Bureau, and indicated that full support would be given the Bureau in carrying forward the program for continued extension and improvement in health services for mothers and children.

During the two-day meeting, members were divided into seven subcommittees to consider special subjects and make such recommendations to the full committees as were indicated. The following abstract of the more than sixty recommendations adopted by the

committees has been prepared for the interest of the pediatricians (copies of the full report of the joint meeting of the two Advisory Committees will be available in the near future):

*Training of Personnel.*—In the deliberations of each subcommittee and in the discussions by the full committees it was quite apparent that there was a unanimity of opinion as to the urgent need for the training of professional personnel as a first step in the development of new programs or in the extension of existing programs. Emphasis was given to the use of regularly established and approved educational institutions for providing such professional training. It was urged that funds be made available to strengthen the essential training programs in recognized educational institutions, and that a closer working relationship be developed between the official agencies administering maternal and child health and crippled children's services, and the educational institutions. Several suggestions were made as a working basis for such cooperative relationships, with the added comment that the arrangements should be such as to safeguard the freedom of the educational institution on the one hand and the administrative responsibility of the State agency on the other. It was also recommended that the State agencies administering maternal and child health and crippled children's services take appropriate steps to encourage and assist the various professional schools in the preparation of professional personnel with reference to the social aspects of health and medical services and for participation in community health services. Special mention was made of the need for training administrative personnel in the health field in order to relieve medical and technical specialists from procedural matters. The committees pointed to the responsibility of the Children's Bureau in exploring training needs and for assisting educational institutions and State agencies in developing cooperative relationships affecting the training of personnel.

*Extension and Improvement of State Services for Crippled Children.*—The advisory committees reaffirmed the recommendations made to the Children's Bureau in December, 1944, calling for expansion of the State services for crippled children. The committees called attention to the special needs of children with rheumatic fever, cerebral palsy, orthodontic defects, speech and hearing defects, epilepsy, and chronic illnesses, but made no recommendation with respect to priority in the development of such services. However, it was recommended in the extension of the State programs to include new services, that these should be developed in a limited area, providing the full range of preventive, diagnostic, and technical services, rather than in a piece-meal manner. Considerable emphasis was given to the importance of safeguarding the quality of care being provided crippled children by maintaining qualification standards for the selection of professional personnel to render services for crippled children and by the State agency conducting periodic impartial reviews of the quality of professional services through the use of committees of qualified specialists. It was also urged that the Children's Bureau undertake evaluation studies of the special programs to determine their effectiveness. The committees recommended that the Children's Bureau conduct a national fact-finding survey to determine the incidence and prevalence of cerebral palsy and other factors affecting the care and treatment of such children. Attention was called to the need for the development of centers in conjunction with approved medical schools for the training of personnel in the care and management of the cerebral palsied child, and a recommendation was adopted that the Children's Bureau use its resources in developing appropriate plans for such training facilities.

*Development of New and Improvement of Existing Services for the Care of Maternity Patients.*—The committees reviewed current problems related to maternity care and recommended that State health departments assist hospitals in establishing blood banks in strategic areas, especially for the benefit of maternity patients. It was also recommended that as hospitals increase their facilities under the hospital construction program, major attention be given to the need for additional hospital maternity facilities. It was suggested that consideration be given also to the advisability of providing annexes for antepartum and postpartum care for patients not requiring full professional care at the hospital. It was the opinion of the committees that every State health department should assure that adequate provisions exist for medical, nursing, medical social and nutrition advisory services to hospitals with maternity services.

It was pointed out that maternity care services and tuberculosis control programs should cooperate in assuring every maternity patient a routine chest x-ray early in pregnancy as a part of her complete prenatal examination.

The Committees urged that State health departments, in cooperation with teaching centers whenever possible, develop obstetric clinical consultation services to general practitioners especially for those residing in rural areas. The committees believed that there should be developed in at least one needy rural area in the United States in cooperation with a medical teaching institution a comprehensive maternity care project. Such a project as visualized by the Committees would assure the highest quality of medical, nursing, nutrition and medical-social services and hospital care, and would be of inestimable value in determining how maternity care of high quality can best be provided in such areas.

The committees recommended that the Children's Bureau prepare and issue for the public a small leaflet outlining the essentials of adequate maternity care and that appropriate steps be taken to assure the widest possible distribution.

*Development and Improvement of Facilities and Services for the Care of the Newborn Infant With Special Reference to Those Prematurely Born.*—The committees gave considerable attention to problems related to the care of prematurely born infants. It was recommended that the birth weight of the infant be reported on all birth certificates and that health departments investigate the cause of each premature birth upon receipt of the birth certificate. It was pointed out that infants weighing  $5\frac{1}{2}$  pounds or less require special premature care. It was urged that several leading medical organizations including the American Academy of Pediatrics endorse the Children's Bureau Publication No. 292, "Standards and Recommendations for Hospital Care of Newborn Infants (Full-term and Premature)" and to use it as a criterion in the investigation of such services in hospitals. It was also recommended that State Health Departments use this publication as a criterion for approving and listing centers for the care of premature infants and where indicated to assist hospitals in establishing or enlarging such facilities.

The Committees recommended that State health departments be encouraged to purchase hospital care, transportation, pediatric, and after-care services for premature infants and for sick, newborn infants in approved centers for infants eligible for such care. Considerable emphasis was given to the importance of developing adequate professional training opportunities for physicians and nurses in the care and management of the newborn infant (premature and term) and it was urged that State health departments assist in financing such an educational program as well as providing pediatric consultation services to physicians and hospitals, in the care of the newborn infant.

*Preschool and School Health Services.*—In considering this important phase of child health services, the committees called attention to the importance of basic public health services on which to build an adequate child health program. It was recommended in view of the present lack of trained personnel, the limitation of funds, and an insufficient body of knowledge concerning the administration of a complete health program for children, that there be developed demonstration projects in which all the health needs of children would be met. As visualized by the conference members such demonstration projects would provide (1) field training of personnel for an expanding program (2) yardsticks for evaluating the effectiveness of the various components of a child health program as well as (3) rendering care of a high quality to the children in the project area. It was stated that those services directed toward the promotion of optimal physical and emotional health would constitute the basis of the program but that in addition the child would have access to complete diagnostic and consultation service and necessary treatment including hospitalization. The committees then listed a series of principles which should be observed in the development of such complete health service projects.

Attention was called to the need for developing model school health legislation in order to overcome the legal barriers which now tend to obstruct future programs in this field.

*Mental Health Services for Children.*—The committees considered the problems presented by the current dearth of trained personnel (psychiatrists, psychologists, and psychiatric social workers) in the face of increasing demands for such personnel. It was felt among the steps

which might be considered at this time in the development of mental health services for children that new child guidance clinics be developed in communities ready for such services, that present training resources be expanded and strengthened and as rapidly as training personnel becomes available new resources for training be developed; that priority for training fellowships be granted to those professional individuals who are potential teachers in this special field; that the training courses for all professional groups engaged in services for children be strengthened and broadened to insure a better understanding of the mental development of children. In this connection the committees also recommended that the Children's Bureau collaborate with the United States Office of Education regarding the inclusion of mental health services in the school health program, and that the Children's Bureau augment its professional staff in the mental health field in order to serve in an advisory and consultative capacity in the development and coordination of mental health services for children.

*Eligibility of Mothers and Children for Services Under State Programs.*—The committees discussed at some length the controversial issues involved pertaining to eligibility requirements for mothers and children seeking services under the State programs. After a thorough discussion the committees unanimously adopted among others the following statement and recommendation: "The widest diversity now exists in different States with regard to basic policies governing eligibility for services under State plans for maternal and child health and crippled children. This diversity is of an extent, which can hardly be justified by existing differences of local conditions in those States. The application of basic principles should be made sufficiently flexible to meet real local limitations and opportunities so long as the fundamental human needs are met."

"One of the most fundamental human rights is the right of every individual to the maximum degree of physical and emotional health which it is possible for that individual to attain with the aid of the best scientific knowledge and technical service which are at the disposal of the Nation."

"Those knowledges and services which deal primarily with the prevention of disease, the promotion of health in the positive sense and the detection of incipient disease form a part of the basic community health program. They should be available for every person and every economic level. In regard to services of this kind, we recommend that the Children's Bureau insist that no means test be permitted in the maternal and child health and crippled children's programs."

"The treatment of disease was considered a problem of a somewhat different nature, although still a problem much more closely related to public health than to poor relief. However, wherever the funds for service of this kind are inadequate for universal coverage, it seems clear that preference should be given to those most in need. In this type of service, your Committee suggests that the Children's Bureau may properly recognize a suitably formulated criteria of economic ability if desired by individual State authorities."

"It is urged that the Bureau encourage the study and eventual development of a pattern whereby the essential medical services may be made available to all, irrespective of residence, race or economic status."

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The letter which follows was sent by Dr. Skinner in midsummer for publication in the column. On receipt of it, I wrote to Dr. Skinner urging him to withdraw it because pediatricians were tired of the controversy it revived and the letter would be productive only of ill feeling. I further pointed out, as editor of the column, the impropriety of the attacks on persons and the use of conjecture for fact. Nevertheless, in order to be absolutely fair in the conduct of the column, I informed Dr. Skinner that I would publish his letter if he insisted that I do so, and he has now written his insistence. Accordingly, I publish Dr. Skinner's letter, but with the understanding that I shall not publish replies which it might awaken.

E. A. P.

Dear Dr. Park:

In the April issue of the JOURNAL OF PEDIATRICS, I noticed the comments of Dr. Martin relative to the brochure, "Stepping Stones to Regimentation," a copy of which I am enclosing. Although I realize there can be endless controversy, it seems no more than fair to me that the medical profession should be made acquainted with the background of this pamphlet.

The EMIC Program was initiated in the State of Washington under the auspices of the State Medical Association. Within a year it was taken completely out of our hands and, what seemed very evident to us, was used as a political extension through the emotional appeal of maternal care. Every iota of successful operation has been realized by hard working physicians who, in a majority of instances carried on under vehement protestations disclaimed by the Children's Bureau.

Before publishing this pamphlet for use of the state, we submitted it in the form of a questionnaire to every practicing physician in the State of Washington with the remarkable return of 32 per cent replies, some of which were quite outstanding in their stinging remarks against bureaucracy. The proposition was twofold, to inform the medical profession of what was clearly evident; the detouring of the use of a patriotic service to further political expansion, and the second, to offer a remedy. It has been the policy of our committee never to criticize without offering some logical remedy. It might be appropriate to state here that this is not the "horse and buggy era" but rather, the jet plane epoch, and it is to be recognized that this period would be of such rapidity that it would too quickly pass through the arc of some persons' intelligence and too soon be outside their ability to comprehend its passing.

It is true the bureau stated again and again that the EMIC Program would end six months after the war terminated, whenever that may be, and also that it was for an emergency only. It is reported that before a session of the executive committee of the Academy of Pediatrics this year Dr. Martha Eliot was pointedly asked if she intended to abide by her promise made again and again "to terminate the EMIC Program six months after the termination of the war." She replied "No!"

This bill is divided into three parts. I am sure that the propositions of the first two parts would meet the approval of every physician except for the fact that it definitely is to be placed without restriction, under bureaucratic administration. The third section concerns not the health, but the direction by force, if the Children's Bureau considers it necessary, to regulate every child socially in the United States from birth to the age of 21 years. It has been pointed out by a probate judge in the State of Michigan, that this is exactly the same method Hitler inaugurated in Germany, and we will be obligated to cope for years to come with the resultant Psychopathy.

That portion of the pamphlet relating to the "appointed advisory committee" is true. At least four members of those committees, two at one time just having come from Washington, D. C., made the statements as printed and we have no reason to question their veracity. We feel that any committee advisory to a bureaucratic setup is not well chosen except by the members of the different state medical associations throughout the United States. It is true that the Academy of Pediatrics is now conducting a very commendable survey of child health service throughout the United States. It is being intimately overseen in this state by the President of the Academy of Pediatrics and others. In addition to this, the Maternal and Child Welfare Committee with the help of the State Health Department, has been conducting an obstetrical survey throughout the State of Washington for at least four years before the war, with the result that we have some excellent records of obstetrical needs which could not be bettered by bureaucratic control and interference.

Whenever a child is sick, whether he be fifty miles from a railroad in Montana or thirty miles from a town in Texas, or in the slums of New York or Chicago, for care, either the doctor goes to him or he must come to his physician. Is there anything that a bureaucracy could stimulate to make this situation better? It is silly to contemplate a bureau in Washington releasing a directive to order the local doctor to visit the child. If the young doctor has been

cared for by the government since birth, and at the age of 21 he has been completely Russianized by the Children's Bureau Educational Scheme he will be perfectly socially minded. Yet will he have Christian compunctions with a respect for the principles of Hippocrates!

Enclosed is another pamphlet about two hundred thousand of which have been distributed mainly through the efforts of the State Medical Women's Auxiliary. Its object, as stated, is to inform the people that the bureau has very definite political designs against the people of the United States, and to offer a remedy. Apparently there are many people in the United States who believe government of the people, by the bureaus, and for the politicians is the best policy.

The so-called health bill, S.1606, was not written by physicians in the interest of United States medical care, but by Arthur Altmeyer and Isadore Falk whose concepts for United States dictatorship are well known. Bill S.1318 smacks so much of the statements and writings of Dr. Martha Eliot, and also directives issued by the Children's Bureau, that we are of the opinion that Senator Pepper never saw the bill until handed by the Bureau. These bills are for political power under the guise of "health service" empowered by the emotional appeal of maternity and child care to age 21! Any obstetrician in our opinion, or pediatrician who favors these bills is out and out for a dictatorship of the United States. This applies both to the physician who is eking out his declining years of service and intelligence in the ample armchair of complacency with sinecure emeritus of an institution, and, the poor struggling pediatrician who is misguided by the above authorities.

H. H. SKINNER, M.D.,  
Chairman, Maternal and Child Welfare Committee

## Academy News and Notes

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The following Fellows of the Academy have been or are about to be released from service:

### *Army*

David H. Clement, New Haven, Conn.  
Harry O. Davidson, Detroit, Mich.  
Albert A. Frank, Malden, Mass.  
Jerome S. Harris, Durham, N. C.  
Oscar B. Markey, Cleveland, Ohio  
Carl L. Ruder, Mt. Lebanon, Pittsburgh, Pa.  
Roland Stahr, Reno, Nev.  
Ralph H. Verploeg, Denver, Colo.

### *Navy*

Fred W. Bush, Rochester, N. Y.  
Marion G. Josephi, San Francisco, Calif.  
Willard B. Rew, Yakima, Wash.  
Proctor C. Waldo, Oak Park, Ill.

*United States Public Health Service and  
United Nations Relief and Rehabilitation Administration*

Stanton Garfield, Concord, Mass.

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Captain Ernest S. V. Laub, Medical Corps, United States Navy, was transferred July 30, 1946, from the Reserve to the Medical Corps of the Navy.



## News and Notes

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The following physicians have been certified by the American Board of Pediatrics following examination by the board in Cleveland, Ohio, and San Francisco, Calif.:

Herman Anfanger, Sixty-Eight Medical Regiment, Camp Forest, Tenn.  
Talcott Bates, Box 107 1, Monterey, Calif.  
Joseph Harold Batzle, Jr., Suite 4, 4205 Market Street, Riverside, Calif.  
Richard Winston Blumberg, Station Hospital, Fort Oglethorpe, Ga.  
Moses R. Buchman, 187 Fox Meadow Road, Scarsdale, N. Y.  
Louise S. Childs, The Clinic, Young Street, Honolulu, Hawaii.  
Homer Tullock Clay, 828 Medical Arts Building, Tacoma, Wash.  
Martha Louise Clifford, 165 Capitol Avenue, Hartford, Conn.  
Peter Cohen, University of California Hospital, San Francisco 22, Calif.  
David Richard Davis, 103 Gazette Building, Emporia, Kan.  
Paul A. di Sant'Agnese 3975 Broadway, New York 32, N. Y.  
Elinor Fosdick Downs, Babies Hospital, One Hundred Sixty-Eighth and Broadway, New York, N. Y.  
Jerome Feldman, 810 East Lincoln Street, Hoopeston, Ill.  
Kurt Glaser, 432 Belmont Avenue, Chicago 14, Ill.  
Percy F. Guy, Medical Dental Building, Seattle, Wash.  
Edward Alun Harris, Employees' Hospital, Fairfield, Ala.  
Scott Thurber Harris, 2900 South Fort Street, Detroit 25, Mich.  
Alexander Hatoff, Permanente Foundation Hospital, Broadway and MacArthur, Oakland 11, Calif.  
William W. Herman, 2350 Ardleigh Drive, Cleveland Heights, Ohio.  
Gertrude E. Howe, 1819 West Polk Street, Chicago, Ill.  
George D. Husser, 322 Twenty-Third Street, Richmond, Calif.  
Owen Austin Kearns, Citizens Bank Building, Monrovia, Calif.  
Pearl Lee, 1071 Stoddard Avenue, San Bernardino, Calif.  
Hyde S. Leland, 16241 Wildemere Avenue, Detroit 21, Mich.  
Leo Litter, 25 Highland Terrace, New Britain, Conn.  
Nina Litton, 99 Bay State Road, Boston, Mass.  
Edward Augustus Loeb, Southern Permanente Hospital, Fontana, Calif.  
Erhard Loewinsohn, 1525 East Fifty-Third Street, Chicago 15, Ill.  
Stanley Louie, 135 Stockton Street, San Francisco 8, Calif.  
Frederick J. Margolis, American National Bank Building, Kalamazoo, Mich.  
Edgar L. Mariette, 136 North Central Avenue, Glendale, Calif.  
David William Martin, 619 Comeau Building, West Palm Beach, Fla.  
George Winford McCormick, 15 Court Street, Staten Island, N. Y.  
Ralph E. Moloshok, 73 East Ninetieth Street, New York, N. Y.  
Marion Shaffner Morse, 134 Washington Avenue, Endicott, N. Y.  
Alexander Sandor Nadas, 31 Federal Street, Greenfield, Mass.  
Henry Bernard Okner, 155 South Pulaski Road, Chicago, Ill.  
William W. Ornduff, 2580 Baneroff Avenue, Berkeley, Calif.  
Edward L. Pratt, 300 Longwood Avenue, Boston 15, Mass.  
Lawrence E. Reck, 3201 Fourth Avenue, San Diego 3, Calif.  
Alexander E. Rostler, 150 Purchase Street, Fall River, Mass.  
Herschel Sachs, 3669 Alter Place, Cincinnati 29, Ohio.  
Edwin Paul Scott, 220 Monohan Drive, Louisville 7, Ky.  
Amelia Burns Sheftall (Geeslin), 1022 Park Street, Jacksonville, Fla.

Bernard Harold Shulman, 1162 Union Street, Brooklyn, N. Y.  
 Harold I. Shuman, 483 Beacon, Boston, Mass.  
 William Benjamin Smith, 1125 Bradbury, Indianapolis, Ind.  
 Margaret Stebbins (Smith), 433 Maple Avenue, Edgewood, Pittsburgh 18, Pa.  
 James T. Stanton, 1930 Truxton Avenue, Bakersfield, Calif.  
 Stuart Shelton Stevenson, 1275 Post Road, Fairfield, Conn.  
 Robert Austin Tidwell, 205 Stimson Building, Seattle, Wash.  
 Stewart C. Wagoner, 1339 Union Street, Schenectady, N. Y.  
 Dr. Wain Newton Walcher, 789 Howard Avenue, New Haven, Conn.  
 Edwin Robeson Watson, United States Marine Hospital, Mobile, Ala.  
 B. H. Williams, Joplin, Mo.  
 Edwin Thurston Williams, 1850 Gilpin Street, Denver, Colo.

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Dr. Kenneth S. Landauer has been appointed director of the division of medical care of the National Foundation of Infantile Paralysis. He will coordinate the organization's year-round program of medical care and treatment of poliomyelitis patients under supervision of Dr. Hart E. Van Riper, medical director.

Dr. Landauer has recently been director of the New York State Reconstruction Home at West Haverstraw and previous to that was director of the Cardiac Bureau of the New York State Health Department. He is a fellow of the American Academy of Pediatrics.

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Senior Fellowships for training in the field of pediatrics, administered by the Medical Fellowship Board of the National Research Council acting for the National Foundation for Infantile Paralysis, Inc., are open to physicians under 40 years of age who are citizens of the United States and who have demonstrated aptitude and promise in teaching and investigation.

These fellowships provide an opportunity, under favorable conditions, for a prolonged period of advanced training in the field of pediatrics. This training may include study and investigation in the basic medical sciences as well as clinical experience. The program throughout the period of appointment will be subject to the approval of the Medical Fellowship Board.

Original appointments are for a term of three years, but fellowships may be renewed at the discretion of the Board for an additional period not to exceed three years. During the term of the fellowship, the holder is not expected to engage in other remunerative work.

The amount of the fellowship is determined by individual circumstances and may vary from \$3,000 to \$6,000 a year. A sum not to exceed \$1,000 annually for laboratory expenses may accompany each fellowship.

Applications for Senior Fellowships should be filed before January 1. Decision concerning awards will be made as soon as practicable after March 1.

Further particulars concerning these fellowships may be obtained on request from the Secretary of the Medical Fellowship Board, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

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The following appointments have been made in recent months, indicating changes in teaching positions in various medical schools of the country:

Dr. Franklin P. Gengenbach of Denver, Colo., has been made emeritus professor of pediatrics in the University of Colorado School of Medicine. He is succeeded by Dr. Harry H. Gordon of New York, N. Y., formerly of the Department of Pediatrics of Cornell University. Dr. Gengenbach has been president of the American Academy of Pediatrics.

Dr. Edwards A. Park has been made emeritus professor of pediatrics at Johns Hopkins University. He is succeeded by Dr. Francis F. Schwentker as professor of pediatrics. Dr. Schwentker has been in the Department of Pediatrics at the Johns Hopkins University.

Dr. Henry F. Helmholtz has retired as professor of pediatrics at the Mayo Foundation and head of the section on pediatrics of Mayo Clinic at Rochester, Minn. He is a former

president of the American Academy of Pediatrics. Dr. Helmholtz is succeeded by Dr. Roger L. J. Kennedy. Dr. Kennedy has been a member of the staff at Mayo Clinic.

Dr. Richard M. Smith has retired as professor of pediatrics at Harvard University Medical School. Dr. Smith has been president of the American Academy of Pediatrics. He is succeeded by Dr. Charles A. Janeway. Dr. Janeway has been a member of the staff of Harvard University Medical School.

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Fellowships leading to a Master's Degree in Public Health in the field of Health Education are being offered to any qualified United States citizen between the ages of 22 and 40, according to a statement released Nov. 12, 1946, by the United States Public Health Service, Federal Security Agency. Tuition, travel expenses for field training, and a stipend of \$100 a month will be provided out of funds furnished by the National Foundation for Infantile Paralysis.

Candidates must hold a Bachelor's Degree from a recognized college or university and must be able to meet the entrance requirements of the accredited school of public health of their choice. In addition to the degree, courses in the biological sciences, sociology, and education may be required. Training in public speaking, journalism, psychology, and work in public health or a related field are considered desirable qualifications.

The year's training, which begins with the 1947 fall term, consists of eight or nine months of academic work including: public health administration, epidemiology, public health and school education, problems in health education, community organization, and information techniques; and three months of supervised field experience in community health education activities.

Application blanks may be obtained by writing to the Surgeon General, United States Public Health Service, Washington 25, D. C., and must be filed prior to March 15, 1947.

Veterans are encouraged to apply and will be paid the difference between their subsistence allowance under the G. I. Bill of Rights and the monthly stipend of \$100. Employees of local and state health departments are not eligible since Federal grants-in-aid are already available for such training purposes.

## Book Reviews

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**Courage and Devotion Beyond the Call of Duty.** Second preliminary Edition. Evansville, Ind., 1946, Mead-Johnson & Co.

The second "preliminary" edition of the record of official citations to medical officers in World War II now contains over 900 individual citations and about fifty group citations. There are still a great number missing, as a local check disclosed. When the book is completed it will be a most valuable and interesting record of the splendid work of the doctors in the armed forces in the late war.

**The Health of the School Child.** Gertrude E. Cromwell, R.N.M.S., Philadelphia, 1946, W. B. Saunders Company, 256 pages. Price \$2.50.

This book contains a little about a great many things. While the purpose is to give a clearer understanding to the nurse, it contains material having to do with school architecture etc., which hardly comes within the function of the nurse. Some sections have been so condensed in order to cover a tremendous field in a brief text that the material is decidedly sketchy. The author has had a vast personal experience and training in school nursing and its relationship to other school activities. It would seem to the reviewer that it would be an excellent text to feed to the lay members of our school boards who, as a whole, are politically minded rather than school minded and have little conception of a school health program.

## Comment

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### THE ACADEMY STUDY OF CHILD HEALTH SERVICES

When the Academy's Committee for the Study of Child Health Services was given the official green light signal at the St. Louis session in November, 1944, the general opinion, as expressed at its first organizational meeting, was that a budget of some \$20,000 to \$25,000 would probably be sufficient to finance a survey of existing child health facilities and services in the United States, and would point up those deficiencies most urgently needing attention upon which a cooperative action program between governmental agencies (particularly the Children's Bureau) and the Academy could be based.

Last month, on October 1, this same committee met in Washington, D. C., to review the progress of the survey and to make plans for the future. It learned that the originally estimated, rather microscopic budget had, in the two-year interval, grown to the adult proportions of around \$1,000,000. How did this tremendous increase in magnitude over the original estimations come about? There are many factors involved, but the main answer is to be found in the kind of job that is being done. This is the first time that a medical organization has ever undertaken a project of this kind. The usual sampling method has not been employed by John Hubbard and his able staff. Actual details have been collected for every city, town, hamlet, and for every county in the United States, concerning hospital facilities, physicians' and dental services, and voluntary and official community health service, both from a quantitative and qualitative point of view. Even the number of telephone calls per day (and night) which the harassed dispenser of child health services must sandwich in between all the other demands upon his time and good nature will be known. In addition to these fundamental questions, Dr. James Wilson is heading another phase of the study which is a thorough inquiry into the status of undergraduate and postgraduate pediatric education as it exists in our medical schools and hospitals today.

When the collection of factual data is completed, some 250,000 schedules will be in the hands of the central office in Washington for statistical analysis and tabulation. Instead of employing one person for a hundred years to do this job, Dr. Hubbard tells us that sixty girls, plus some miraculous machines that need only a few minor adjustments to raise them to human levels, will complete the task in approximately six months. Obviously, when the statistical portion of the study is completed, there will be available a tremendous volume of factual data concerning facilities and services for children as well as the deficiencies in various areas. Already it can be said that this portion of the survey is an assured success.

If, at this point, we begin to wonder whether this huge investment, largely of other people's money which has been invested in the Academy's study, plus

the time and effort of a great many people, is worth the price, let us see what others think. The National Foundation for Infantile Paralysis has backed us by an outright grant of some \$116,000, and many thousands of dollars more have been given by local chapters in the various states. For the first time in its history, the National Institute of Health has departed from its established custom of restricting its funds to purely scientific projects to assign a sizeable sum (\$128,000) to a social study. The Field Foundation, Mead Johnson and Company, Lederle Laboratories, Inc., M & R Dietetic Laboratories, Inc., Pet Milk Company, and Carnation Company have all demonstrated their confidence in the Academy's project by making substantial contributions. Without the very generous and especially skilled aid of the U. S. Public Health Service and the Children's Bureau, the study would not have been possible. This harmonious and effective attack upon an important national health problem by a combination of governmental agencies and physicians is a real achievement pointing the way to the solution of the problem of improving the health facilities and services for all our people. And last but not least, there are the state chairmen who, together with their executive secretaries and pediatric confreres, have done and are doing a magnificent job in the actual collection of data at the local level. The combined State budget which these state chairmen have raised amounts to approximately \$450,000. At Washington it was the good fortune of the members of the National Committee to observe the state chairmen in session at the third of the regional conferences. Each of us, I am sure, was impressed and stimulated by the enthusiasm and determination which was manifest on every hand. All this adds up to the inescapable conclusion that a great many important people have confidence in the project the Academy has taken on. Is it worth while? These people think so, and they have backed up their belief with their dollars and with their personal participation. That every Academy member believes so, there is not the slightest doubt. Furthermore, I am certain that all of us in the Academy fully realize the responsibility, the opportunity, and the challenge which faces us in order that those who have reposed their confidence in us are not let down. The information which has been collected in the survey must be implemented into an action program, or much of the effort which has gone into the statistical phase of the study will have been wasted. The Academy has no intention of letting such a catastrophe come to pass.

The greater portion of the Committee's deliberations in Washington was concerned, not with the survey itself, but with the utilization of the factual data which will be available some time late in 1947 or early in 1948. It was the feeling of the present Committee that its function would come to an end with the publication of the statistical material at both national and state levels. A recommendation is being made to the Executive Board of the Academy that a new representative Committee be established and charged with the responsibility of interpretation of the collected data, setting up standards for comparison purposes at any given locale, and even more fundamental, preparing the blueprints for a long-time, cooperative action program designed to achieve the mutually desired objective stated in the Academy's first report; namely, "To make available to all mothers and children of the United States all essential preventive,

diagnostic, and curative medical services of high quality, which, used in cooperation with other services for children, will make this country an ideal place for children to grow into responsible citizens."

Many of us objected to the government-sponsored bills introduced into the last session of Congress on the grounds of political domination, unworkability, likelihood of lowering standards of medical practice, probability of abolishment of private practice, and antagonism and therefore noncooperation on the part of the general medical profession in what it was felt was "socialized medicine." Furthermore, there was the additional objection that none of these proposed bills bore any relation to specifically demonstrated needs.

The survey being completed offers a new approach to the whole problem of improvement of child health. Facts, and many of them, are going to be made known about deficiencies in facilities and services, facts which have been obtained by physicians themselves. In correcting these deficiencies, legislation is going to be needed, but it will be legislation with a known purpose, based on these facts. There is every reason to believe that the Academy and the governmental agencies which have cooperated so splendidly in the statistical analysis will, in the same sort of a joint effort, go forward in the next phase of the program--implementation and action.

The conclusion that ought to be reached, it seems to me, is that instead of completing a task it set out to do, the Academy has but taken the first step. True, that first step has been a big one and an important one, but there must follow many more steps equally vigorous and equally important.

LEE FORREST HILL

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